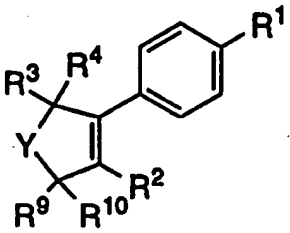




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/CA96/00306  <b>(22) International Filing Date:</b> 15 May 1996 (15.05.96)  <b>(30) Priority Data:</b> 08/443,620 18 May 1995 (18.05.95) US  <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US 08/443,620 (CIP) Filed on 18 May 1995 (18.05.95)  <b>(71) Applicant (for all designated States except US):</b> MERCK FROSST CANADA INC. [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BLACK, Cameron [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). GRIMM, Erich [DE/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). WANG, Zhaoyin [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). LEGER, Serge [CA/CA];	16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA).  <b>(74) Agent:</b> MURPHY, Kevin, P.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College, Montreal, Quebec H3A 2Y3 (CA).  <b>(81) Designated States:</b> AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>	
<b>(54) Title:</b> DIARYL-5-OXYGENATED-2-(5H)-FURANONES AS COX-2 INHIBITORS		
<b>(57) Abstract</b>  <p>The invention encompasses the novel compound of Formula (I) as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula (I). The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of Formula (I).</p> <div style="text-align: center;">  <p>(I)</p> </div>		

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**TITLE OF THE INVENTION****DIARYL-5-OXYGENATED-2-(5H)-FURANONES AS COX-2  
INHIBITORS****5 BACKGROUND OF THE INVENTION**

This invention relates to methods of treating cyclooxygenase mediated diseases and certain pharmaceutical compositions therefor.

Non-steroidal, antiinflammatory drugs exert most of their  
1 0 antiinflammatory, analgesic and antipyretic activity and inhibit  
hormone-induced uterine contractions and certain types of cancer  
growth through inhibition of prostaglandin G/H synthase, also known as  
cyclooxygenase. Initially, only one form of cyclooxygenase was known,  
1 5 this corresponding to cyclooxygenase-1 (COX-1) or the constitutive  
enzyme, as originally identified in bovine seminal vesicles. More  
recently the gene for a second inducible form of cyclooxygenase,  
cyclooxygenase-2 (COX-2), has been cloned, sequenced and  
characterized initially from chicken, murine and human sources. This  
enzyme is distinct from the cyclooxygenase-1 which has been cloned,  
2 0 sequenced and characterized from various sources including the sheep,  
the mouse and man. The second form of cyclooxygenase,  
cyclooxygenase-2, is rapidly and readily inducible by a number of  
agents including mitogens, endotoxin, hormones, cytokines and growth  
factors. As prostaglandins have both physiological and pathological  
2 5 roles, we have concluded that the constitutive enzyme, cyclooxygenase-  
1, is responsible, in large part, for endogenous basal release of  
prostaglandins and hence is important in their physiological functions  
such as the maintenance of gastrointestinal integrity and renal blood  
flow. In contrast, we have concluded that the inducible form,  
3 0 cyclooxygenase-2 (COX-2), is mainly responsible for the pathological  
effects of prostaglandins where rapid induction of the enzyme would  
occur in response to such agents as inflammatory agents, hormones,  
growth factors, and cytokines. Thus, a selective inhibitor of  
cyclooxygenase-2 will have similar antiinflammatory, antipyretic and

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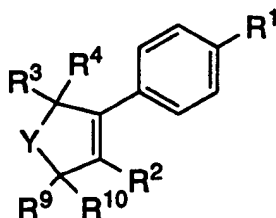
analgesic properties to a conventional non-steroidal antiinflammatory drug, and in addition would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects.

- 5 In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

A brief description of the potential utilities of  
10 cyclooxygenase-2 inhibitors is given in an article by John Vane, Nature, Vol. 367, pp. 215-216, 1994 and in an article in Drug News and Perspectives, Vol. 7, pp. 501-512, 1994.

### SUMMARY OF THE INVENTION

- 15 The invention encompasses the novel compound of Formula I as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I.



20

I

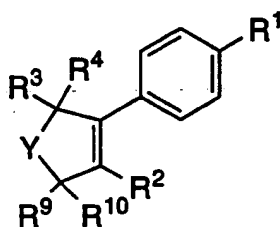
The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases, comprising compounds of Formula I.

### 25 DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses the novel compound of Formula I as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I.

30

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I

or a pharmaceutically acceptable salt thereof  
wherein:

5 Y is selected from the group consisting of

- (a) C(R<sup>11</sup>)(R<sup>12</sup>),
- (b) oxygen,
- (c) sulfur,

R<sup>1</sup> is selected from the group consisting of

- 10 (a) S(O)<sub>2</sub>CH<sub>3</sub>,
- (b) S(O)<sub>2</sub>NH<sub>2</sub>,
- (c) S(O)<sub>2</sub>NHC(O)CF<sub>3</sub>,
- (d) S(O)(NH)NH<sub>2</sub>,
- (e) S(O)(NH)NHC(O)CF<sub>3</sub>,
- 15 (f) S(O)<sub>2</sub>NHMe
- (g) P(O)(CH<sub>3</sub>)NH<sub>2</sub>,
- (h) P(O)(CH<sub>3</sub>)<sub>2</sub>,
- (i) C(S)NH<sub>2</sub>

20 R<sup>2</sup> is selected from the group consisting of

- (a) C<sub>1</sub>-10alkyl,
- (b) C<sub>3</sub>-10cycloalkyl,
- (c) C<sub>2</sub>-10alkenyl
- (d) C<sub>2</sub>-10alkynyl
- 25 (e) C<sub>3</sub>-10cycloalkenyl
- (f) mono-, di-, tri- or tetra-substituted C<sub>3</sub>-C<sub>10</sub>cycloalkenyl  
wherein the substituent is selected from the group  
consisting of
- (1) halo,
- 30 (2) C<sub>1</sub>-6alkoxy,

- 4 -

- 5
- (3) C<sub>1-6</sub>alkylthio,  
 (4) CN,  
 (5) CF<sub>3</sub>,  
 (6) C<sub>1-10</sub>alkyl,  
 (7) N<sub>3</sub>,  
 (8) -CO<sub>2</sub>H,  
 (9) -CO<sub>2</sub>-C<sub>1-10</sub>alkyl,  
 (10) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,  
 (11) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-4</sub>alkyl, and  
 10 (12) -C<sub>1-10</sub>alkyl-CO<sub>2</sub>-R<sup>5</sup>;  
 (13) benzyloxy,  
 (14) -O-(C<sub>1-10</sub>alkyl)-CO<sub>2</sub>R<sup>5</sup>,  
 (15) -O-(C<sub>1-10</sub>alkyl)-NR<sup>5</sup>R<sup>6</sup>,
- 15 (g) unsubstituted or mono-, di- or tri-substituted phenyl or  
 naphthyl wherein the substituent is selected from the group  
 consisting of
- 20 (1) C<sub>1-10</sub>alkyl,  
 (2) C<sub>1-10</sub>alkoxy,  
 (3) C<sub>1-10</sub>fluoroalkoxy,  
 (4) C<sub>1-10</sub>alkylthio,  
 (4) CN,  
 (6) CF<sub>3</sub>,  
 (7) halo,  
 (8) N<sub>3</sub>,  
 25 (9) -CO<sub>2</sub>H,  
 (10) -CO<sub>2</sub>-C<sub>1-10</sub>alkyl,  
 (11) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,  
 (12) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-4</sub>alkyl, and  
 (13) -C<sub>1-6</sub>alkyl-CO<sub>2</sub>-R<sup>5</sup>;  
 30 (14) benzyloxy,  
 (15) -O-(C<sub>1-10</sub>alkyl)-CO<sub>2</sub>R<sup>5</sup>,  
 (16) -O-(C<sub>1-10</sub>alkyl)-NR<sup>5</sup>R<sup>6</sup>,
- (h) unsubstituted or mono-, di- or tri-substituted heteroaryl  
 wherein the heteroaryl is a monocyclic aromatic ring of 5

- 5 -

- atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms, said substituents being selected from the group consisting of
- (1) C<sub>1-10</sub>alkyl,
  - (2) C<sub>1-10</sub>alkoxy,
  - (3) C<sub>1-10</sub>alkylthio,
  - (4) CN,
  - (5) CF<sub>3</sub>,
  - (6) halo,
  - (7) N<sub>3</sub>,
  - (8) -CO<sub>2</sub>H,
  - (9) -CO<sub>2</sub>-C<sub>1-10</sub>alkyl,
  - (10) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,
  - (11) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-4</sub>alkyl, and
  - (12) -C<sub>1-6</sub>alkyl-CO<sub>2</sub>-R<sup>5</sup>;
  - (13) benzyloxy,
  - (14) -O-(C<sub>1-10</sub>alkyl)-CO<sub>2</sub>R<sup>5</sup>,
  - (15) -O-(C<sub>1-10</sub>alkyl)-NR<sup>5</sup>R<sup>6</sup>,
- (i) an unsubstituted or a mono-, di-, tri- or tetra-substituted benzoheterocycle in which the heterocycle is a 5, 6, or 7-membered ring which may contain 1 or 2 heteroatoms chosen independently from O, S, or N and which may contain a carbonyl group or a sulfonyl group; the said substituents are selected from the group consisting of
- (1) C<sub>1-10</sub>alkyl,
  - (2) C<sub>1-10</sub>alkoxy,
  - (3) C<sub>1-10</sub>alkylthio,
  - (4) CN,
  - (5) CF<sub>3</sub>,
  - (6) halo,
  - (7) N<sub>3</sub>,

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- (8) -CO<sub>2</sub>H,  
(9) -CO<sub>2</sub>-C<sub>1-10</sub>alkyl,  
(10) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,  
(11) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-4</sub>alkyl, and  
5 (12) -C<sub>1-6</sub>alkyl-CO<sub>2</sub>-R<sup>5</sup>;  
(13) benzyloxy,  
(14) -O-(C<sub>1-10</sub>alkyl)-CO<sub>2</sub>R<sup>5</sup>,  
(15) -O-(C<sub>1-10</sub>alkyl)-NR<sup>5</sup>R<sup>6</sup>,
- (j) a heterocycloalkyl group of 5, 6 or 7 members which  
10 contains 1 or 2 heteroatoms chosen from O, S, or N and  
optionally contains a carbonyl group or a sulfonyl group.
- (k) an unsubstituted or a mono- or di- substituted  
benzocarbocycle in which the carbocycle is a 5, 6, or 7-  
membered ring which optionally contains a carbonyl group,  
15 the said substituents are selected from the group consisting  
of  
(1) C<sub>1-10</sub>alkyl,  
(2) C<sub>1-10</sub>alkoxy,  
(3) C<sub>1-10</sub>alkylthio,  
20 (4) CN,  
(5) CF<sub>3</sub>,  
(6) halo,  
(7) N<sub>3</sub>,  
(8) -CO<sub>2</sub>H,  
25 (9) -CO<sub>2</sub>-C<sub>1-10</sub>alkyl,  
(10) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,  
(11) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-4</sub>alkyl, and  
(12) -C<sub>1-6</sub>alkyl-CO<sub>2</sub>-R<sup>5</sup>;  
(13) benzyloxy,  
30 (14) -O-(C<sub>1-10</sub>alkyl)-CO<sub>2</sub>R<sup>5</sup>,  
(15) -O-(C<sub>1-10</sub>alkyl)-NR<sup>5</sup>R<sup>6</sup>,

R<sup>3</sup> is hydrogen, C<sub>1-10</sub>alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, or C<sub>1-6</sub>fluoroalkyl, F, CONR<sup>7</sup><sub>2</sub>, unsubstituted or mono- or di-substituted phenyl, unsubstituted or mono or di-substituted benzyl, unsubstituted or



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mono- or di-substituted heteroaryl, unsubstituted or mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

- |    |   |
|----|---|
| 5  | (1) C <sub>1-10</sub> alkyl,  |
|    | (2) C <sub>1-10</sub> alkoxy,   |
|    | (3) C <sub>1-10</sub> alkylthio,  |
|    | (4) CN,   |
|    | (5) CF <sub>3</sub> ,   |
|    | (6) halo,   |
| 10 | (7) N <sub>3</sub> ,  |
|    | (8) -CO <sub>2</sub> H,   |
|    | (9) -CO <sub>2</sub> -C <sub>1-10</sub> alkyl,                          |
|    | (10) -C(R <sup>5</sup> )(R <sup>6</sup> )-OH,                           |
|    | (11) -C(R <sup>5</sup> )(R <sup>6</sup> )-O-C <sub>1-4</sub> alkyl, and |
| 15 | (12) -C <sub>1-6</sub> alkyl-CO <sub>2</sub> -R <sup>5</sup> ;          |
|    | (13) benzyloxy,   |
|    | (14) -O-(C <sub>1-10</sub> alkyl)-CO <sub>2</sub> R <sup>5</sup> ,      |
|    | (15) -O-(C <sub>1-10</sub> alkyl)-NR <sup>5</sup> R <sup>6</sup> ,      |

R<sup>4</sup> is

- |    |   |
|----|---|
| 20 | (a) C <sub>1-10</sub> alkoxy,             |
|    | (b) C <sub>1-10</sub> alkylthio,          |
|    | (c) C <sub>1-10</sub> fluoroalkoxy,       |
|    | (d) -OH,                                  |
|    | (e) -OCOR <sup>7</sup> ,                  |
| 25 | (f) -SH,                                  |
|    | (g) -SCOR <sup>7</sup> ,                  |
|    | (h) -OCO <sub>2</sub> R <sup>8</sup> ,    |
|    | (i) -SCO <sub>2</sub> R <sup>8</sup> ,    |
|    | (j) OCONR <sup>7</sup> <sub>2</sub> , and |
| 30 | (k) SCONR <sup>7</sup> <sub>2</sub> ;     |
|    | (l) C <sub>3-10</sub> cycloalkoxy,        |
|    | (m) C <sub>3-10</sub> cycloalkylthio;     |
|    | (n) -NR <sup>7</sup> <sub>2</sub> ;       |

each R<sup>5</sup> or R<sup>6</sup> is independently selected from the group consisting of

- 8 -

- (a) hydrogen, and  
(b) C<sub>1-10</sub>alkyl,  
or R<sup>5</sup> and R<sup>6</sup> together with the carbon to which they are attached  
form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7  
atoms;

5

each R<sup>7</sup> is independently selected from the group consisting of

- (a) hydrogen and  
(b) R<sup>8</sup>;

each R<sup>8</sup> is independently selected from the group consisting of

10

- (a) C<sub>1-10</sub>alkyl,  
(b) phenyl or monosubstituted phenyl wherein the substituents  
may be halo, C<sub>1-10</sub>alkyl, C<sub>1-10</sub>alkoxy, C<sub>1-10</sub>alkylthio,  
CN, or CF<sub>3</sub>,

15

- (c) benzyl or monosubstituted benzyl wherein the substituents  
may be halo, C<sub>1-10</sub>alkyl, C<sub>1-10</sub>alkoxy, C<sub>1-10</sub>alkylthio,  
CN, or CF<sub>3</sub>, and

- (d) C<sub>3-10</sub>cycloalkyl

R<sup>9</sup> and R<sup>10</sup> are independently selected from the group consisting of:

20

- (a) hydrogen,  
(b) C<sub>1-10</sub>alkyl,  
(c) C<sub>3-10</sub>cycloalkyl, or

R<sup>9</sup> and R<sup>10</sup> together form a double bonded O or S;

R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of:

25

- (a) hydrogen ,  
(b) unsubstituted or mono- or di-substituted phenyl or  
unsubstituted or mono- or di-substituted benzyl or  
unsubstituted or mono- or di-substituted heteroaryl, or  
unsubstituted or mono- or di-substituted heteroarylmethyl,  
said substituents being selected from the group consisting  
of:

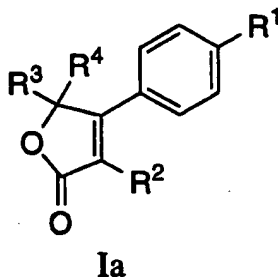
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- (1) C<sub>1-10</sub>alkyl,  
(2) C<sub>1-10</sub>alkoxy,  
(3) C<sub>1-10</sub>alkylthio,  
(4) CN,

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- (5)  $\text{CF}_3$ ,  
 (6) halo,  
 (7)  $\text{N}_3$ ,  
 (8)  $-\text{CO}_2\text{H}$ ,  
 5 (9)  $-\text{CO}_2\text{-C}_{1-10}\text{alkyl}$ ,  
 (10)  $-\text{C}(\text{R}^5)(\text{R}^6)\text{-OH}$ ,  
 (11)  $-\text{C}(\text{R}^5)(\text{R}^6)\text{-O-C}_{1-4}\text{alkyl}$ , and  
 (12)  $-\text{C}_{1-6}\text{alkyl-CO}_2\text{-R}^5$ ;  
 (13) benzyloxy,  
 10 (14)  $-\text{O-(C}_{1-10}\text{alkyl)-CO}_2\text{R}^5$ ,  
 (15)  $-\text{O-(C}_{1-10}\text{alkyl)-NR}^5\text{R}^6$ ,  
 (c)  $\text{C}_{1-10}\text{alkyl}$ ,  $\text{CH}_2\text{OR}^7$ ,  $\text{CN}$ ,  $\text{CH}_2\text{CN}$ ,  $\text{C}_{1-10}\text{fluoroalkyl}$ ,  $\text{F}$  or  $\text{CONR}^7_2$ ; or  
 $\text{R}^{11}$  and  $\text{R}^{12}$  together with the carbon to which they are attached  
 15 form a carbonyl or a saturated monocyclic carbon ring of  
 3, 4, 5, 6 or 7 atoms;  
 $\text{R}^{13}$  and  $\text{R}^{14}$  are independently selected from the group consisting of:  
 (a) hydrogen,  
 (b)  $\text{C}_{1-10}\text{alkyl}$ , or  
 20  $\text{R}^{13}$  and  $\text{R}^{14}$  together with the carbon to which they are attached  
 form a carbonyl,  $-\text{C}(=\text{S})-$ , or a saturated monocyclic carbon  
 ring of 3, 4, 5, 6, or 7 atoms.

In one genus this invention is directed to compounds of the  
 25 formula



wherein:

- $\text{R}^1$  is selected from the group consisting of  
 30 (a)  $\text{S(O)}_2\text{CH}_3$ ,

- 10 -

- (b)  $\text{S(O)}_2\text{NH}_2$ ,
- (c)  $\text{S(O)}_2\text{NHC(O)CF}_3$ ,
- (d)  $\text{S(O)(NH)NH}_2$ ;

$\text{R}^2$  is selected from the group consisting of

- 5                    unsubstituted or mono-, di- or tri-substituted phenyl  
                      wherein the substituent is selected from the group  
                      consisting of
- (1) halo,
  - (2)  $\text{C}_{1-4}$ alkoxy,
  - 10                    (3)  $\text{C}_{1-4}$ alkylthio,
  - (4) CN,
  - (5)  $\text{CF}_3$ ,
  - (6)  $\text{C}_{1-4}$ alkyl,
  - (7)  $\text{N}_3$ ,
  - 15                    (8)  $-\text{C(R}^5\text{)(R}^6\text{)-OH}$ ,

$\text{R}^3$  is hydrogen,  $\text{C}_{1-4}$ alkyl,  $\text{CH}_2\text{OR}^7$ , CN,  $\text{CH}_2\text{CN}$ , or  $\text{C}_{1-4}$ fluoroalkyl,  
 F,  $\text{CONR}^7_2$ ;

$\text{R}^4$  is

- 20                    (a)  $\text{C}_{1-4}$ alkoxy,
- (b)  $\text{C}_{1-4}$ alkylthio,
  - (c)  $-\text{OH}$ ,
  - (d)  $-\text{OCOR}^7$ ,
  - (e)  $-\text{SH}$ ,
  - 25                    (f)  $-\text{SCOR}^7$ ,
  - (g)  $-\text{OCO}_2\text{R}^8$ ,
  - (h)  $-\text{SCO}_2\text{R}^8$ ,
  - (i)  $\text{OCONR}^7_2$ , and
  - (j)  $\text{SCONR}^7_2$ ;

30    each  $\text{R}^5$  or  $\text{R}^6$  is independently selected from the group consisting of

- (a) hydrogen, and
- (b)  $\text{C}_{1-4}$ alkyl,

each  $\text{R}^7$  is independently selected from the group consisting of

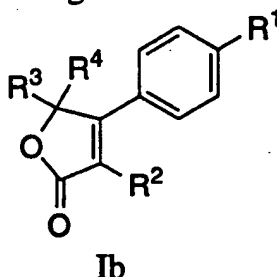
- 35                    (a) hydrogen and
- (b)  $\text{R}^8$ ;

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each R<sup>8</sup> is independently selected from the group consisting of

- (a) C<sub>1</sub>-4alkyl,
- (b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkoxy, C<sub>1</sub>-4alkylthio, CN, or CF<sub>3</sub>;
- (c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkoxy, C<sub>1</sub>-4alkylthio, CN, or CF<sub>3</sub>. and

Within this this genus are the compounds of formula Ib



wherein:

R<sup>1</sup> is selected from the group consisting of

- (a) S(O)<sub>2</sub>CH<sub>3</sub>,
- (b) S(O)<sub>2</sub>NH<sub>2</sub>,

R<sup>2</sup> is selected from the group consisting of

unsubstituted or mono-, di- or tri-substituted phenyl wherein the substituent is selected from the group consisting of

- (1) halo,
- (2) C<sub>1</sub>-3alkoxy,
- (3) CF<sub>3</sub>,
- (4) C<sub>1</sub>-3alkyl,

R<sup>3</sup> is hydrogen, C<sub>1</sub>-3alkyl, CH<sub>2</sub>OR<sup>7</sup>, C<sub>1</sub>-4fluoroalkyl;

R<sup>4</sup> is

- (a) C<sub>1</sub>-3alkoxy,
- (b) C<sub>1</sub>-3alkylthio,
- (c) -OH,
- (d) -OCOR<sup>7</sup>,

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- (e) -SCOR<sup>7</sup>,
- (f) OCONR<sup>7</sup><sub>2</sub>, and
- (g) SCONR<sup>7</sup><sub>2</sub>;

each R<sup>7</sup> is independently selected from the group consisting of

- 5 (a) hydrogen and
  - (b) R<sup>8</sup>;
- each R<sup>8</sup> is C<sub>1-3</sub>alkyl.

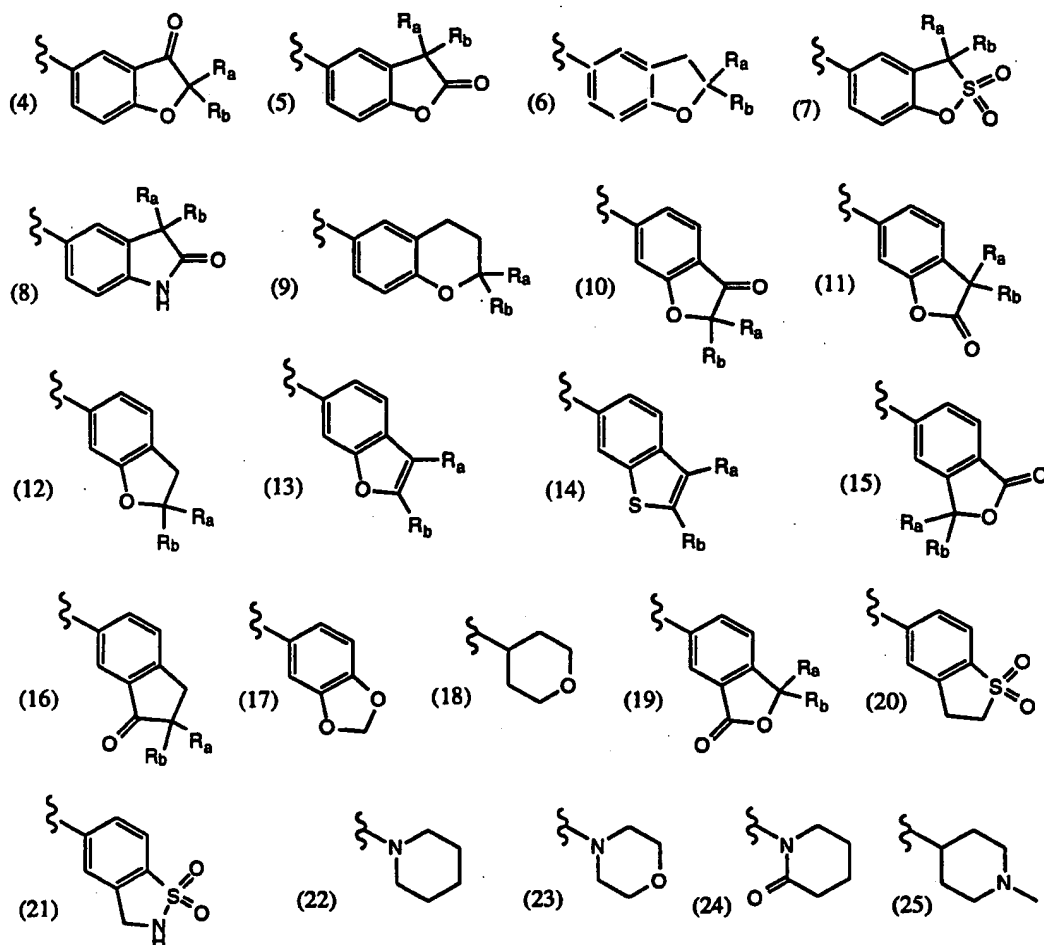
For purposes of this specification heteroaryl as in R<sup>2</sup> is  
10 intended to include, but is not limited to optionally mono- or di-  
substituted

- (1) furanyl,
- (2) diaziny, triaziny, tetraziny,
- (3) imidazolyl,
- 15 (4) isooxazolyl,
- (5) isothiazolyl,
- (6) oxadiazolyl,
- (7) oxazolyl,
- (8) pyrazolyl,
- 20 (9) pyrrolyl,
- (10) thiadiazolyl,
- (11) thiazolyl,
- (12) thienyl,
- (13) triazolyl, or
- 25 (14) tetrazolyl.

Similarly, for purposes of this specification cyclic groups  
such as a heterocycloalkyl or benzocarbocycle or benzoheterocycle such  
as in R<sup>2</sup> is intended to include, but is not limited to optionally mono- or  
30 di-substituted

- (1) indolyl,
- (2) benzofuranyl,
- (3) benzothienyl,

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in which the substituents comprise  $R_a$  and  $R_b$  and said substituents are selected from hydrogen, halo, -OH,  $CF_3$ , C1-3alkoxy, C1-3alkylthio, and C1-3alkyl.

5 One genus of compounds of formula I is that in which  $R^9$  and  $R^{10}$  form a double-bonded O, and Y is O.

For purposes of this specification, alkyl is defined to include linear and branched structures of the indicated number of carbon atoms, including, but not restricted to, methyl, ethyl, propyl, 2-propyl, n-, i-, s- and t-butyl, pentyl, hexyl, 1,1-dimethylethyl, and decyl.

Cycloalkyl means an alkyl group of the indicated number of carbon atoms containing one or more rings anywhere in the structure; examples of cycloalkyl are cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-norbornyl, 1-adamantyl and the like.

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Fluoroalkyl includes alkyl groups of the indicated number of carbon atoms of a straight or branched configuration, in which one or more hydrogen is replaced by fluorine. Examples are -CH<sub>2</sub>F, -CHF<sub>2</sub>, -CF<sub>3</sub>, -CH<sub>2</sub>CF<sub>3</sub>, n-C<sub>9</sub>H<sub>18</sub>CF<sub>3</sub>, -CH(CF<sub>3</sub>)<sub>2</sub>, and the like.

5 Cyclofluoroalkyl includes fluoroalkyl groups of the indicated number of carbon atoms, containing one or more rings anywhere in the structure, in which one or more hydrogen is replaced by fluorine. Examples are c-pr-F<sub>5</sub>, c-hex-F<sub>11</sub>, and the like.

Alkenyl means linear and branched alkenyl groups of the  
10 indicated number of carbon atoms. Examples of alkenyl groups are allyl, 5-decen-1-yl, 2-dodecen-1-yl, 2-ethyl-1-buten-1-yl, and the like.

Cycloalkenyl means alkenyl groups of the indicated number of carbon atoms, containing one or more rings anywhere in the structure, and in which the alkenyl double bond may be located  
15 anywhere in the structure. Examples of cycloalkenyl groups are cyclopropen-1-yl, cyclohexen-3-yl, 2-vinyladamant-1-yl, 5-methylenedodec-1-yl, and the like.

Alkynyl means linear and branched alkynyl groups of the indicated number of carbon atoms. Examples of alkynyl groups are  
20 ethynyl, 2-pentadecyn-1-yl, 1-eicosyn-1-yl, and the like.

Cycloalkynyl means alkynyl groups of 5 or more carbon atoms, which include a ring. The alkynyl triple bond may be located anywhere in the group, with the proviso that if it is within a ring, such a ring must be 10 members or greater. Examples of cycloalkynyl are  
25 cyclododecyn-3-yl, 3-cyclohexyl-1-propyn-1-yl, and the like.

Similarly, alkoxy is intended to include alkoxy groups of the indicated number of carbon atoms of a straight or branched configuration. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, and the like.

30 Cycloalkoxy means an alkoxy group of the indicated number of carbon atoms containing one or more rings anywhere in the structure; examples of cycloalkoxy are cyclopropyloxy, cyclopropylmethoxy, cyclobutoxy, cyclopentyloxy, cyclohexyloxy, 2-norbornyloxy, 1-adamantyloxy, and the like.



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Likewise, alkylthio is intended to include alkylthio groups of the indicated number of carbon atoms of a straight or branched configuration. Examples of alkylthio groups include methylthio, n-propylthio, isopropylthio, decylthio, etc. By way of illustration, the n-propylthio group signifies -SCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>.

Cycloalkylthio means an alkylthio group of the indicated number of carbon atoms containing one or more rings anywhere in the structure; examples of cycloalkylthio are cyclopropylthio, cyclopropylmethylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, 2-norbornylthio, 1-adamantylthio, and the like.

Fluoroalkoxy includes alkoxy groups of the indicated number of carbon atoms of a straight or branched configuration, in which one or more hydrogen is replaced by fluorine. Examples are -OCH<sub>2</sub>F, -OCHF<sub>2</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -O-n-C<sub>9</sub>H<sub>18</sub>CF<sub>3</sub>, -OCH(CF<sub>3</sub>)<sub>2</sub>, and the like.

Cyclofluoroalkoxy means an alkoxy group of the indicated number of carbon atoms containing one or more rings anywhere in the structure, and in which one or more hydrogen is replaced by fluorine; examples of cyclofluoroalkoxy are c-C<sub>3</sub>F<sub>5</sub>O-, c-C<sub>3</sub>F<sub>5</sub>CH<sub>2</sub>O-, C<sub>6</sub>F<sub>11</sub>O, and the like.

Fluoroalkylthio includes alkylthio groups of the indicated number of carbon atoms of a straight or branched configuration, in which one or more hydrogen is replaced by fluorine. Examples are -SCH<sub>2</sub>F, -SCHF<sub>2</sub>, -SCF<sub>3</sub>, -SCH<sub>2</sub>CF<sub>3</sub>, -S-n-C<sub>9</sub>H<sub>18</sub>CF<sub>3</sub>, -SCH(CF<sub>3</sub>)<sub>2</sub>, and the like.

Cyclofluoroalkylthio means an alkylthio group of the indicated number of carbon atoms containing one or more rings anywhere in the structure, and in which one or more hydrogen is replaced by fluorine; examples of cyclofluoroalkylthio are c-C<sub>3</sub>F<sub>5</sub>S-, c-C<sub>3</sub>F<sub>5</sub>CH<sub>2</sub>S-, C<sub>6</sub>F<sub>11</sub>S, and the like. Halo includes F, Cl, Br, or I. Heteroaryl includes furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,3-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3,4-triazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, pyridine, pyridazine,

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pyrimidine, pyrazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, and the like. The term aryl refers to both all-carbon (e.g. benzene, naphthalene) or heteroaryl aromatic rings.

As will be appreciated by those of skill in the art, when a substituent (e.g. alkyl, aryl, R<sup>1</sup> through R<sup>14</sup>, etc.) occurs more than one time in a variable or in formula I, its definition at one occurrence is independent of its definition at every other occurrence. For example, in CONR<sup>7</sup><sub>2</sub>, the two R<sup>7</sup>'s need not be simultaneously the same, although each selection must be consistent with the markush group defining R<sup>7</sup>.

Exemplifying the invention are:

- (1) Benzoic acid, 3-(4-(methylsulfonyl)phenyl)-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester,
- (2) 5-Hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,
- (3) 5-Hydroxy-3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (4) 5-Hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,
- (5) 3-(4-Fluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (6) 3-(4-Chlorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (7) 3-(3,4-Difluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (8) 3-(3-Fluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (9) 3-(3,5-Difluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (10) 5-Methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,
- (11) 3-(4-Chlorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (12) 3-(3,4-Difluorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

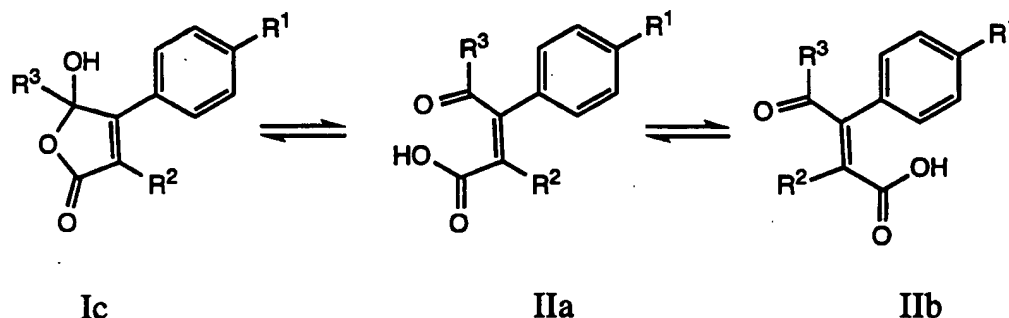
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- 5 (13) 3-(3-Fluorophenyl)-5-methoxy-5-methyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone,  
(14) 3-(3,5-Difluorophenyl)-5-methoxy-5-methyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone,  
(15) 3-(4-Fluorophenyl)-5-methoxy-5-methyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone,  
(16) 5-Ethoxy-3-(4-fluorophenyl)-5-methyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone,  
10 (17) 3-(4-Fluorophenyl)-5-methyl-4-(4-methylsulfonyl)phenyl)-5-propoxy-2-(5H)-furanone,  
(18) 3-(4-Fluorophenyl)-5-isopropoxy-5-methyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone,  
(19) 5-Methyl-5-methylthio-4-(4-methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,  
15 (20) 5-Ethylthio-5-methyl-4-(4-methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,  
(21) 5-Ethyl-5-hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,  
(22) 5-Ethyl-3-(3-fluorophenyl)-5-hydroxy-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone,  
20 (23) Acetic acid, 3-(4-(methylsulfonyl)phenyl)-2-methyl-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester  
(24) 5-Hydroxy-5-methyl-4-((4-methylsulfonyl)phenyl)-3-(2-naphthyl)-2-(5H)-furanone,  
25 (25) Sodium 2-(4-fluorophenyl)-3-((4-methylsulfonyl)phenyl)-4-oxo-2-pentenoate, and  
(26) Sodium 2-(4-chlorophenyl)-3-((4-methylsulfonyl)phenyl)-4-oxo-2-pentenoate.

30 Some of the compounds of Formula I of the present invention in which  $R^4 = OH$  may exist in a tautomeric open chain keto-acid form of Formula IIa or IIb below, depending on the substituents at  $R^1$ ,  $R^2$ , or  $R^3$  or the pH. In such cases, the rate of equilibration may vary, and activity may reside with either tautomer. In particular, it may

be possible to form a salt of compound Ic with a base, said salt existing predominantly in the tautomeric form IIa. Thus, structures IIa and IIb are within the scope of Formula I.

5



10

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

15

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

20

In a second embodiment, the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase and for treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

25

Within this embodiment the invention encompasses pharmaceutical compositions for inhibiting COX-2 and for treating COX-2 mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

30

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In a third embodiment, the invention encompasses a method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases, advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 as disclosed herein comprising:  
5 administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a  
10 pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases  
15 include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of  
20 primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-  
25 ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

30 When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, adipic, aspartic, 1,5-naphthalenedisulfonic, benzenesulfonic, benzoic, camphorsulfonic, citric, 1,2-ethanedisulfonic, ethanesulfonic,

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ethylenediaminetetraacetic, fumaric, glucoheptonic, gluconic, glutamic, hydriodic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, 2-naphthalenesulfonic, nitric, oxalic, pamoic, pantothenic, phosphoric, pivalic, propionic, salicylic, stearic, 5 succinic, sulfuric, tartaric, p-toluenesulfonic acid, undecanoic, 10-undecenoic, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, methanesulfonic, phosphoric, sulfuric and tartaric acids.

It will be understood that in the discussion of methods of  
1 0 treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The Compound of Formula I is useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, 1 5 common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries, following surgical and dental procedures. In addition, such a 2 0 compound may inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be used in the treatment of cancer. Compound I may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumour angiogenesis.

2 5 Compound I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, and for the prevention of bone loss 3 0 (treatment of osteoporosis).

By virtue of its high COX-2 inhibitory activity and/or its specificity for COX-2 over COX-1, Compound I will prove useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such non-steroidal antiinflammatory

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drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia  
5 or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

Similarly, Compound I, will be useful as a partial or complete substitute for conventional NSAID'S in preparations wherein they are presently co-administered with other agents or ingredients.  
1 0 Thus in further aspects, the invention encompasses pharmaceutical compositions for treating COX-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients  
1 5 such as another pain reliever including acetaminophen or phenacetin; a potentiator including caffeine; an H<sub>2</sub>-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive including codeine, hydrocodone,  
2 0 caramiphen, carbetapentane, or dexamethorphan; a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effect amount of the compound of Formula I, optionally  
2 5 co-administered with one or more of such ingredients as listed immediately above.

For the treatment of any of these cyclooxygenase mediated diseases Compound I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations  
3 0 containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-

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blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating COX-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed



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with water or miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting

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agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also  
5 be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol  
10 anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxy-ethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening  
15 agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using  
20 those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed  
25 are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or  
30 diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compound I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating

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excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, gels, solutions or  
5 suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

10 Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the  
15 compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of  
20 administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between  
25 from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

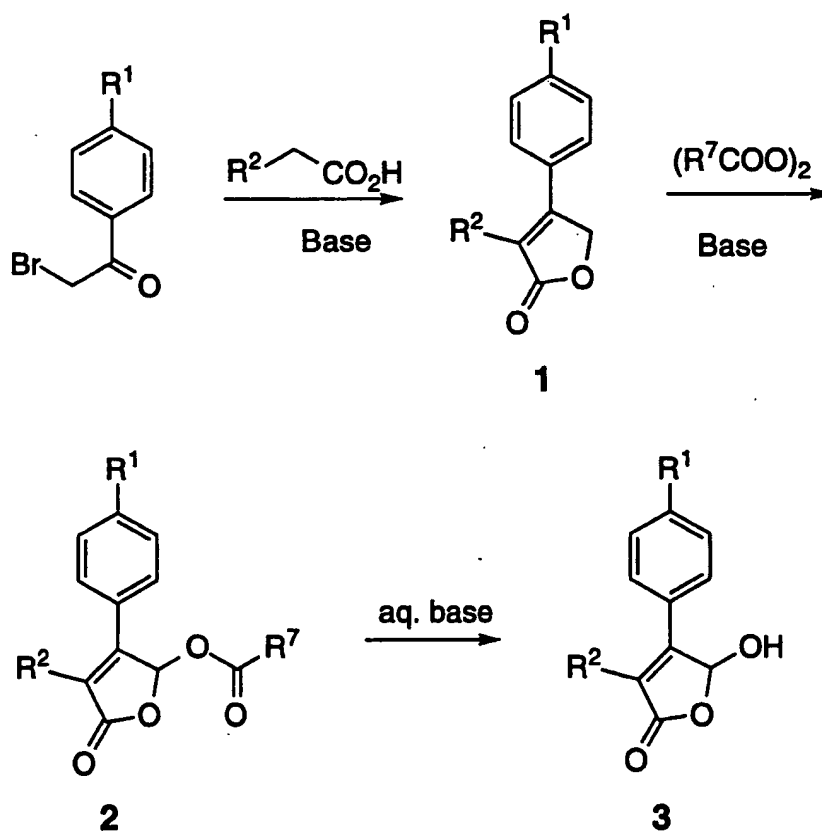
It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors  
30 including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

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The compounds of the present invention can be prepared according to the following methods.

Method A

- 5 An appropriately substituted aryl bromomethyl ketone is reacted with an appropriately substituted aryl acetic acid in a solvent such as acetonitrile in the presence of a base such as triethylamine and then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford lactone **1**. Further treatment of **1** with DBU, followed by  $(R^7COO)_2$ ,  
10 provides ester **2**, which can then be hydrolyzed with aqueous base to give hemiacetal **3**.



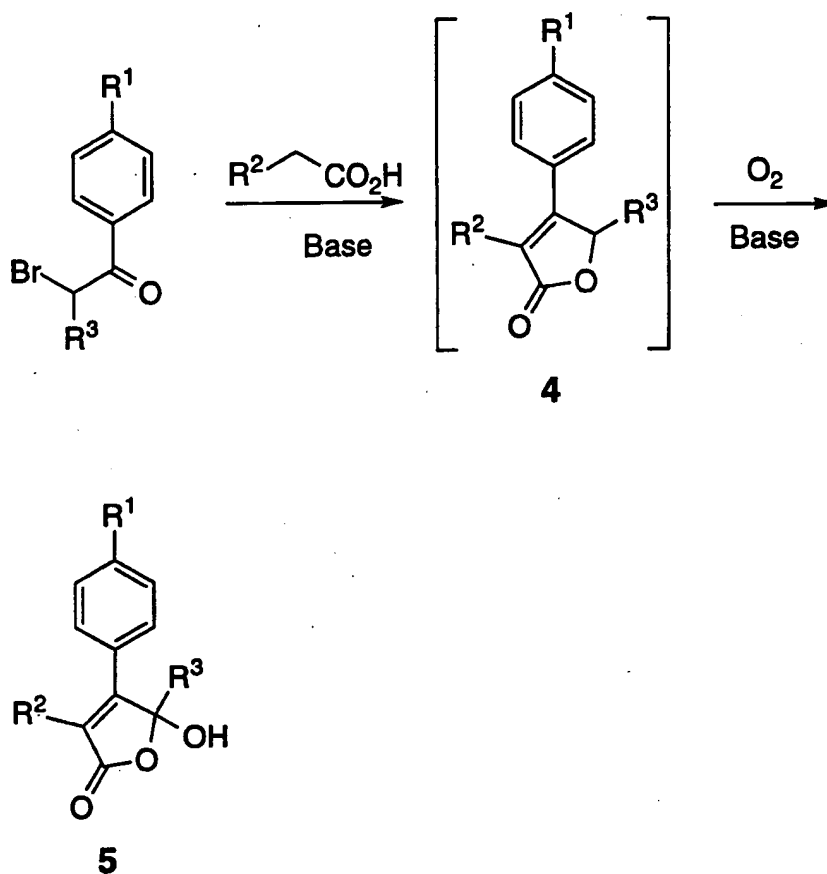
15 Method B

An appropriately substituted aryl bromoketone is reacted with an appropriately substituted aryl acetic acid in a solvent such as

- 27 -

acetonitrile in the presence of a base such as triethylamine and then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford lactone **4** and the crude reaction mixture can then be exposed to excess oxygen until **4** is completely oxidized to hemiketal **5**.

5

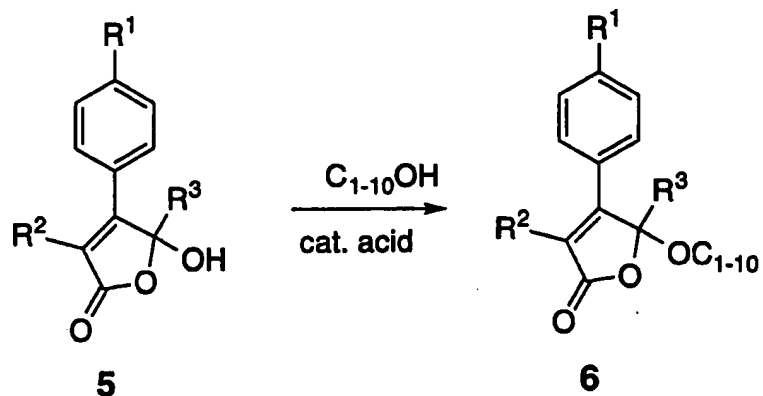


### Method C

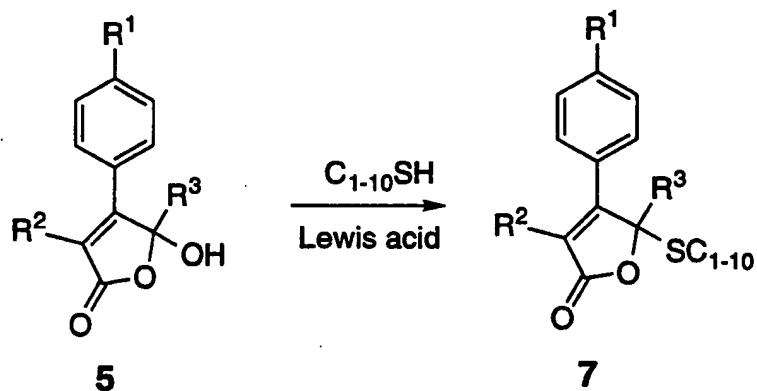
Hemiketal **5** is heated in an appropriate alcohol in the presence of a catalytic amount of acid such as  $H_2SO_4$  to afford ketal **6**.

10

- 28 -

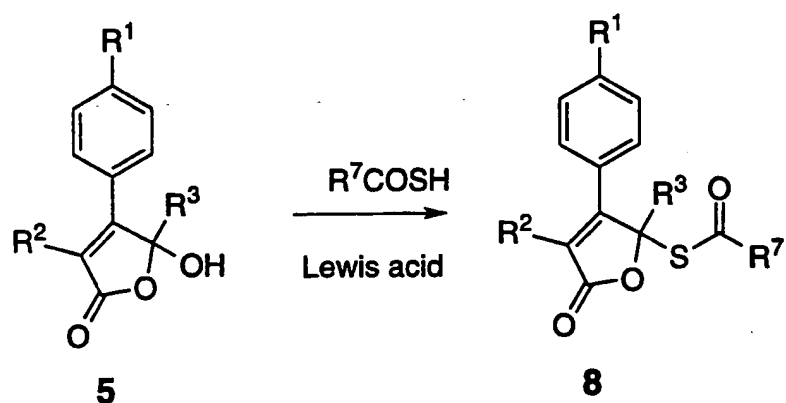
**Method D**

5 Hemiketal **5** is treated with an appropriate thiol in the presence of a Lewis acid such as  $\text{Et}_2\text{O} \cdot \text{BF}_3$  to afford thioketal **7**.

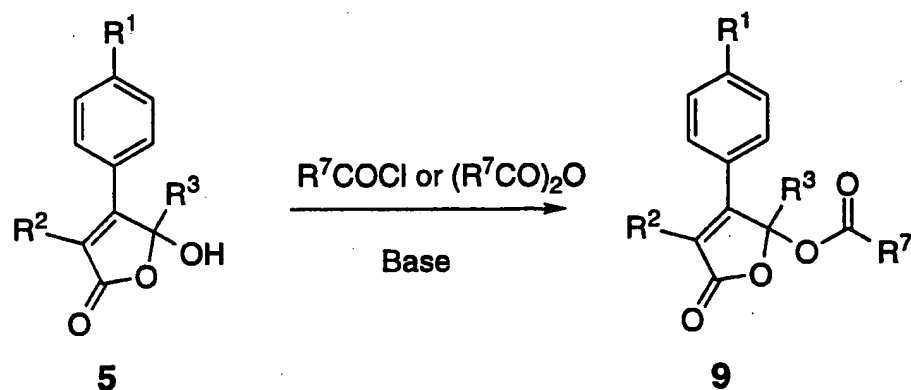
**Method E**

10 Hemiketal **5** is treated with an appropriate thio acid in the presence of a Lewis acid such as  $\text{Et}_2\text{O} \cdot \text{BF}_3$  to afford thioketal **8**.

- 29 -

**Method F**

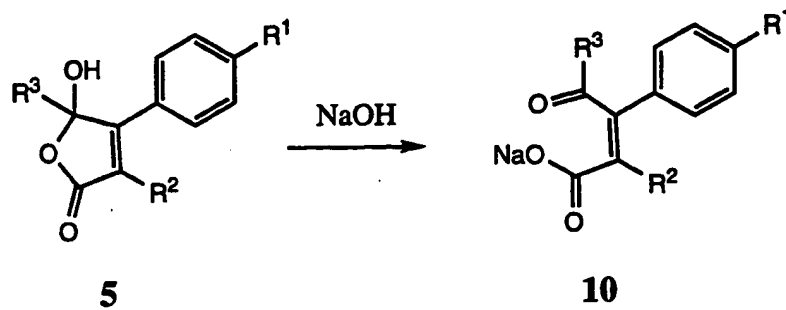
5 Hemiketal **5** is treated with an appropriate acid chloride or anhydride in the presence of a base to afford ketal **9**

**METHOD G**

10

Hemiketal **5** is suspended in EtOH and treated with one equivalent of NaOH. The solvent is evaporated, and the salt is dissolved in water and freeze-dried to provide keto-carboxylate **10**.

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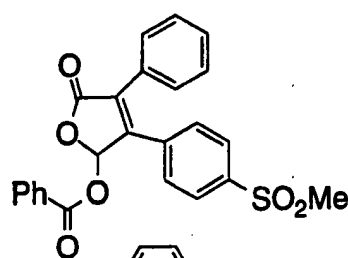
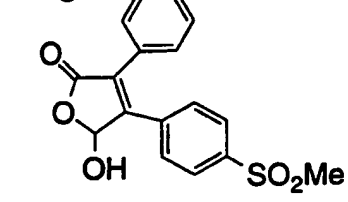
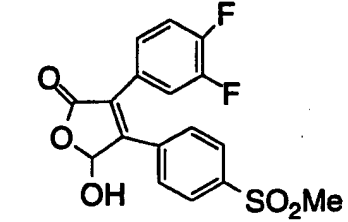
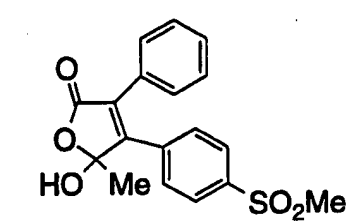
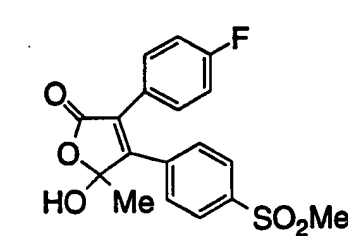
Compounds 2, 3, 5, 6, 7, 8, 9 and 10 are representatives of  
5 structures of the present invention.



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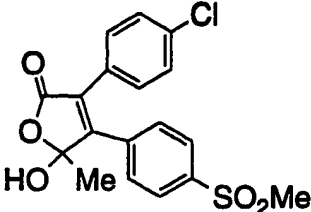
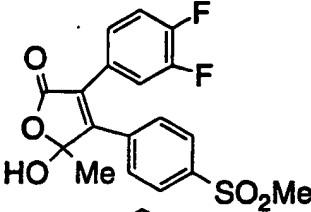
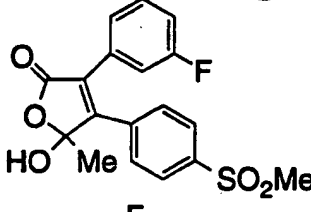
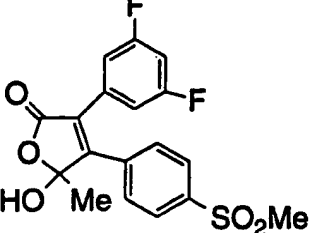
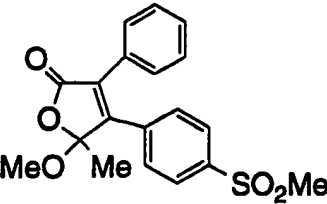
Tables I illustrates novel compounds of the present invention.

Table I

	Example	Method
	1	A
	2	A
	3	A
	4	B
	5	B

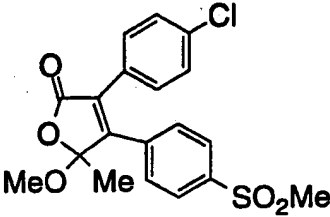
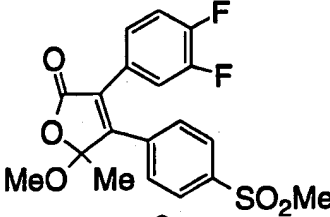
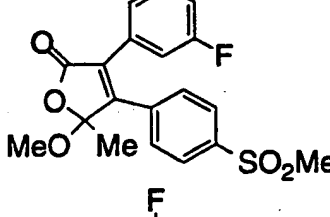
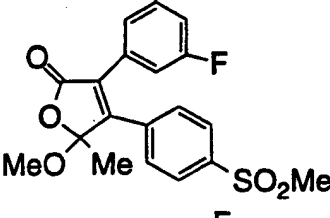
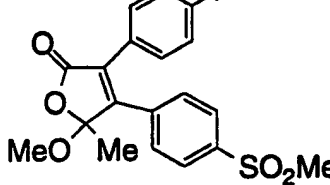
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Table I (continued)

	Example	Method
	6	B
	7	B
	8	B
	9	B
	10	C

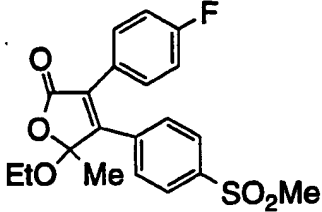
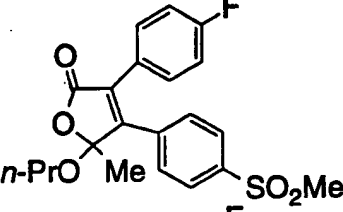
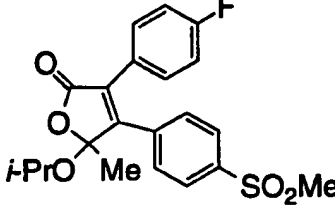
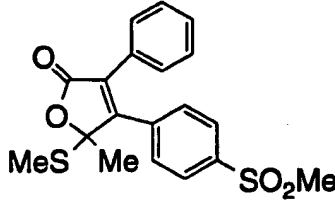
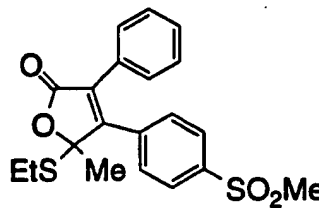
- 33 -

Table I (continued)

	Example	Method
	11	C
	12	C
	13	C
	14	C
	15	C

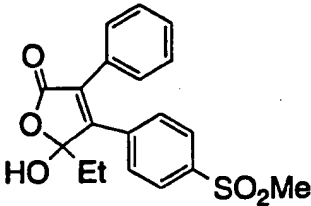
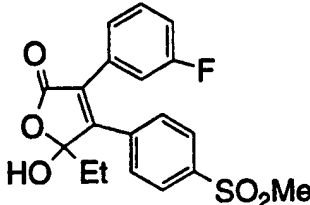
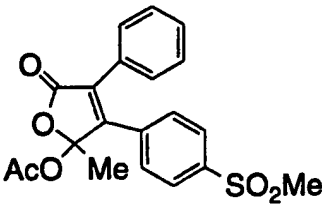
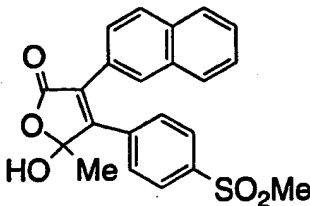
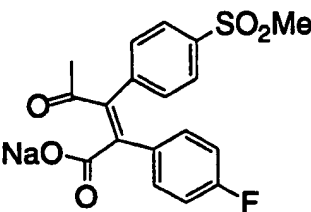
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Table I (continued)

	Example	Method
	16	C
	17	C
	18	C
	19	D
	20	D

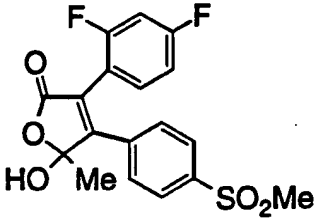
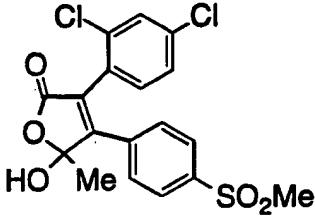
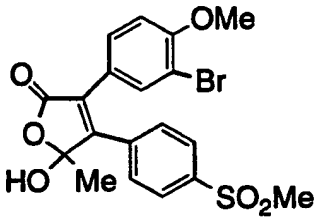
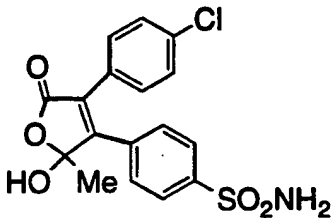
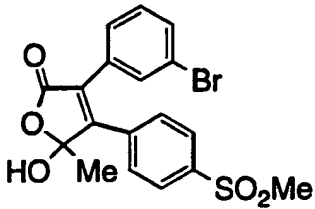
- 35 -

Table I (continued)

	Example	Method
	21	B
	22	B
	23	F
	24	B
	25	G

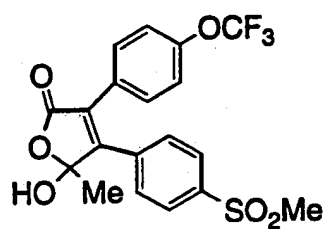
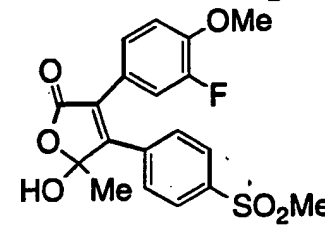
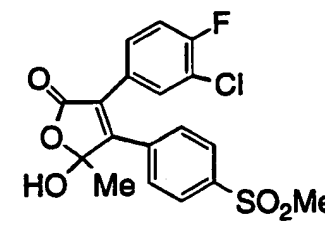
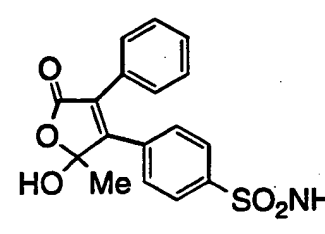
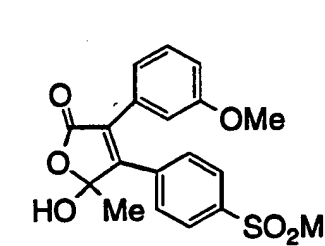
- 36 -

Table I (continued)

	Example	Method
	26	B
	27	B
	28	B
	29	B
	30	B

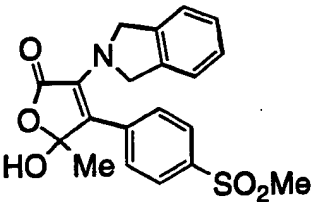
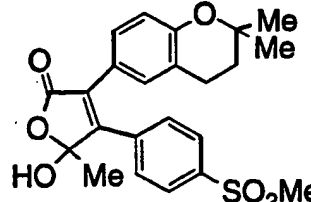
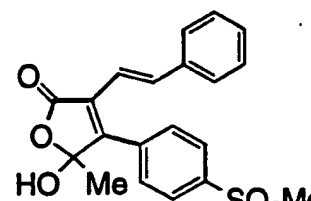
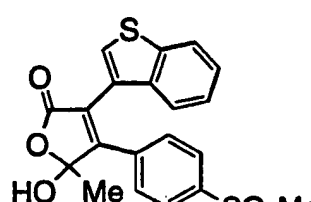
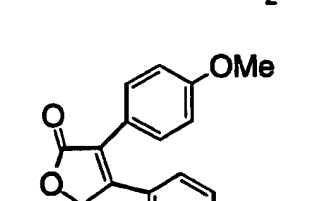
- 37 -

Table I (continued)

	Example	Method
	31	B
	32	B
	33	B
	34	B
	35	B

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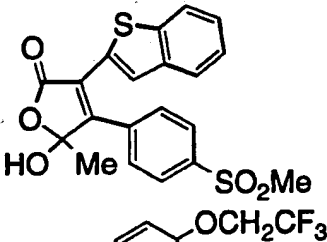
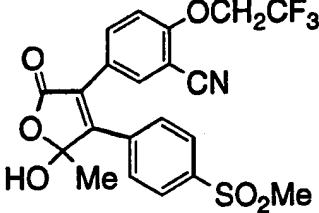
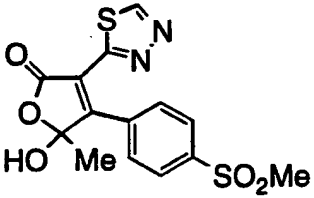
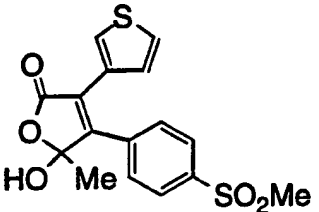
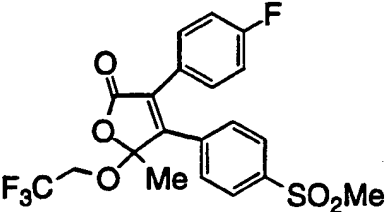
Table I (continued)

	Example	Method
	36	B
	37	B
	38	B
	39	B
	40	B



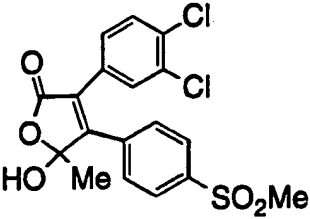
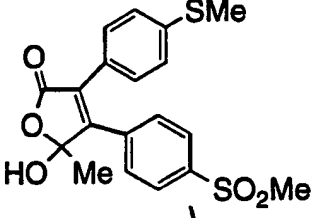
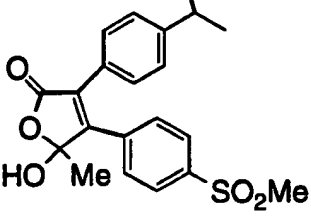
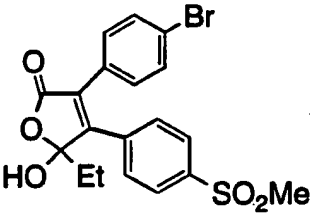
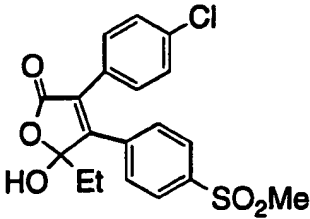
- 39 -

Table I (continued)

	Example	Method
	41	B
	42	B
	43	B
	44	B
	45	C

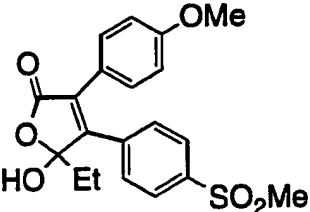
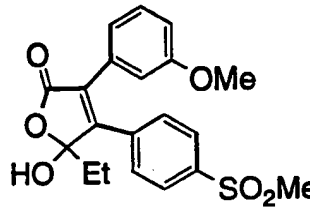
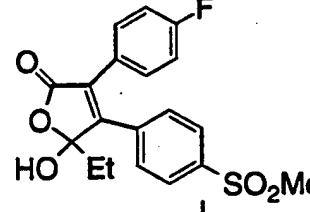
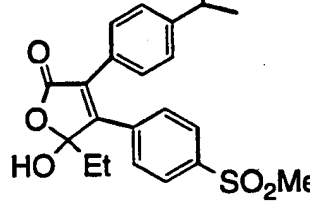
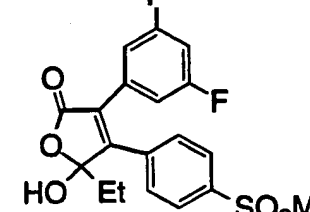
- 40 -

Table I (continued)

	Example	Method
	46	B
	47	B
	48	B
	49	B
	50	B

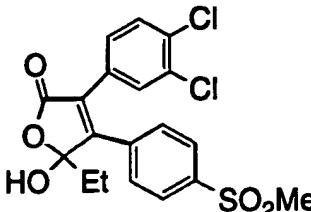
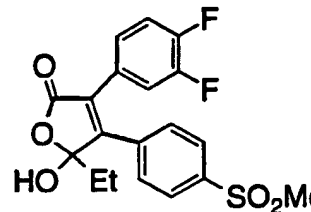
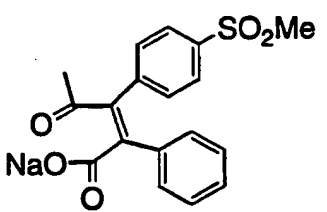
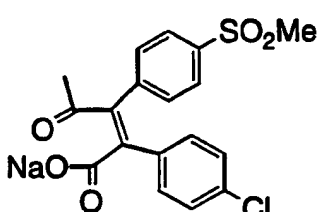
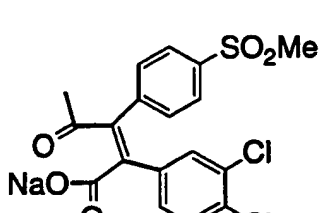
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Table I (continued)

	Example	Method
	51	B
	52	B
	53	B
	54	B
	55	B

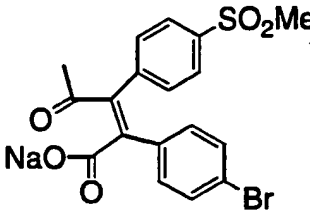
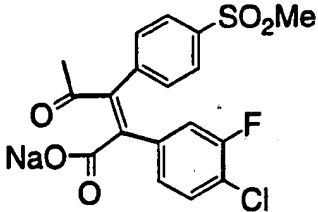
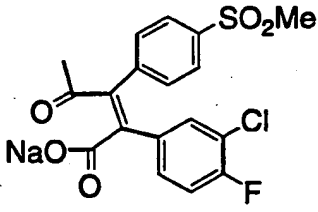
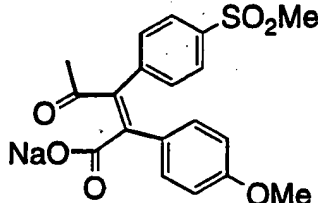
- 42 -

Table I (continued)

	Example	Method
	56	B
	57	B
	58	G
	59	G
	60	G

- 43 -

Table I (continued)

	Example	Method
	61	G
	62	G
	63	G
	64	G

Assays for determining Biological Activity

5 The compound of Formula I can be tested using the following assays to determine their cyclooxygenase-2 inhibiting activity.

Inhibition of Cyclooxygenase Activity

10 Compounds were tested as inhibitors of cyclooxygenase activity in whole cell cyclooxygenase assays. Both of these assays measured prostaglandin E<sub>2</sub> synthesis in response to A.A., using a radioimmunoassay. Cells used for these assays were human osteosarcoma 143 cells (which specifically express COX-2) and human

- 44 -

U-937 cells (which specifically express COX-1). In these assays, 100% activity is defined as the difference between prostaglandin E<sub>2</sub> synthesis in the absence and presence of arachidonate.

5    Assay

For cyclooxygenase assays, osteosarcoma cells are cultured in 1 mL of media in 24-well multidishes (Nunc) until confluent ( $1-2 \times 10^5$  cells/well). U-937 cells are grown in spinner flasks and resuspended to a final density of  $1.5 \times 10^6$  cells/mL in 24-well multidishes (Nunc). Following washing and resuspension of osteosarcoma and U-937 cells in 1 mL of HBSS, 1  $\mu$ L of a DMSO solution of test compound or DMSO vehicle is added, and samples gently mixed. All assays are performed in triplicate. Samples are then incubated for 5 or 15 minutes at 37°C, prior to the addition of A.A..

15    A.A. (peroxide-free, Cayman Chemical) is prepared as a 10 mM stock solution in ethanol and further diluted 10-fold in HBSS. An aliquot of 10  $\mu$ L of this diluted solution is added to the cells to give a final A.A. concentration of 10  $\mu$ M. Control samples are incubated with ethanol vehicle instead of A.A. Samples are again gently mixed and incubated

20    for a further 10 min at 37°C. For osteosarcoma cells, reactions are then stopped by the addition of 100  $\mu$ L of 1N HCl with mixing and by the rapid removal of the solution from cell monolayers. For U-937 cells, reactions are stopped by the addition of 100  $\mu$ L of 1N HCl with mixing. Samples are then neutralized by the addition of 100  $\mu$ L of 1N NaOH and

25    PGE<sub>2</sub> levels measured by radioimmunoassay.

Rat Paw Edema Assay - Protocol

Male Sprague-Dawley rats (150 - 200 g) were fasted overnight and were given po either vehicle (1% methocel or 5% Tween

30    80) or a test compound. One hr later, a line was drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume (V<sub>0</sub>) was measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals were then injected

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subplantarily with 50  $\mu$ l of 1% carrageenan solution in saline (FMC Corp, Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e. 500  $\mu$ g carrageenan per paw). Three hr later, the paw volume ( $V_3$ ) was measured and the increases in paw volume ( $V_3 - V_0$ ) were calculated. The animals were sacrificed by CO<sub>2</sub> aphyxiation and the absence or presence of stomach lesions scored. Data were compared with the vehicle-control values and percent inhibition calculated. ED<sub>50</sub> values were used for comparison. All treatment groups were coded to eliminate observer bias.

10

### NSAID-Induced Gastrophathy in Rats

#### Rationale

The major side effect of conventional NSAIDs is their ability to produce gastric lesions in man. This action is believed to be caused by inhibition of COX-1 in the gastrointestinal tract. Rats are particularly sensitive to the actions of NSAIDs. In fact, rat models have been used commonly in the past to evaluate the gastrointestinal side effects of current conventional NSAIDs. In the present assay, NSAID-induced gastrointestinal damage is observed by measuring fecal <sup>51</sup>Cr excretion after systemic injection of <sup>51</sup>Cr-labeled red blood cells. Fecal <sup>51</sup>Cr excretion is a well-established and sensitive technique to detect gastrointestinal integrity in animals and man.

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### Methods

Male Sprague Dawley rats (150 - 200 g) are administered orally a test compound either once (acute dosing) or b.i.d. for 5 days (chronic dosing). Immediately after the administration of the last dose, the rats are injected via a tail vein with 0.5 mL of  $^{51}\text{Cr}$ -labeled red blood cells from a donor rat. The animals are placed individually in metabolism cages with food and water *ad lib*. Feces are collected for a 48 h period and  $^{51}\text{Cr}$  fecal excretion is calculated as a percent of total injected dose.

$^{51}\text{Cr}$ -labeled red blood cells are prepared using the following procedures. Ten mL of blood is collected in heparinized tubes via the vena cava from a donor rat. Plasma is removed by centrifugation and replenished with equal volume of HBSS. The red blood cells are incubated with 400  $\mu\text{Ci}$  of sodium  $^{51}\text{Cr}$  chromate for 30 min at 37°C. At the end of the incubation, the red blood cells are washed twice with 20 mL HBSS to remove free sodium  $^{51}\text{Cr}$  chromate. The red blood cells are finally reconstituted in 10 mL HBSS and 0.5 mL of the solution (about 20  $\mu\text{Ci}$ ) is injected per rat.

### Protein-Losing Gastropathy in Squirrel Monkeys

#### Rationale

Protein-losing gastropathy (manifested as appearance of circulating cells and plasma proteins in the GI tract) is a significant and dose-limiting adverse response to standard NSAIDs. This can be quantitatively assessed by intravenous administration of  $^{51}\text{CrCl}_3$  solution. This isotopic ion can avidly bind to cell and serum globins and cell endoplasmic reticulum. Measurement of radioactivity appearing in feces collected for 24 h after administration of the isotope thus provides a sensitive and quantitative index of protein-losing gastropathy.

#### Methods

Groups of male squirrel monkeys (0.8 to 1.4 kg) are treated by gavage with either 1% methocel or 5% Tween 80 in H<sub>2</sub>O



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vehicles, (3 mL/kg b.i.d.) or test compounds at doses from 1 - 100 mg/kg b.i.d. for 5 days. Intravenous  $^{51}\text{Cr}$  (5  $\mu\text{Ci/kg}$  in 1 mL/kg PBS) is administered 1 h after the last drug/vehicle dose, and feces collected for 24 h in a metabolism cage and assessed for excreted  $^{51}\text{Cr}$  by gamma-counting. Venous blood is sampled 1 h and 8 h after the last drug dose, and plasma concentrations of drug measured by RP-HPLC.

#### Human Whole Blood (HWB) Assay

##### 10 Rationale

Human whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as selective COX-2 inhibitors. Studies have shown that normal human blood does not contain the COX-2 enzyme. This is consistent with the observation that COX-2 inhibitors have no effect on PGE<sub>2</sub> production in normal blood. These inhibitors are active only after incubation of human whole blood with LPS (lipopolysaccharide), which induces COX-2. This assay can be used to evaluate the inhibitory effect of selective COX-2 inhibitors on PGE<sub>2</sub> production. As well, platelets in whole blood contain a large amount of the COX-1 enzyme. Immediately following blood clotting, platelets are activated through a thrombin-mediated mechanism. This reaction results in the production of thromboxane B<sub>2</sub> (TxB<sub>2</sub>) via activation of COX-1. Thus, the effect of test compounds on TxB<sub>2</sub> levels following blood clotting can be examined and used as an index for COX-1 activity. Therefore, the degree of selectivity by the test compound can be determined by measuring the levels of PGE<sub>2</sub> after LPS induction (COX-2) and TxB<sub>2</sub> following blood clotting (COX-1) in the same assay.

##### 30 METHOD

###### A. COX-2 (LPS-induced PGE<sub>2</sub> production)

Fresh blood was collected in heparinized tubes by venipuncture from both male and female volunteers. The subjects had no apparent inflammatory conditions and had not taken any NSAIDs for

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at least 7 days prior to blood collection. Plasma was immediately obtained from a 2mL blood aliquot to use as blank (basal levels of PGE<sub>2</sub>). The remaining blood was incubated with LPS (100 µg/ml final concentration, Sigma Chem, #L-2630 from E. coli; diluted in 0.1%  
5 BSA-Phosphate buffered saline) for 5 minutes at room temperature. Five hundred µL aliquots of blood were incubated with either 2 µL vehicle (DMSO) or 2 µL of a test compound at final concentrations varying from 10nM to 30µM for 24 hours at 37°C. At the end of the incubation, the blood was centrifuged at 12,000 x g for 5 minutes to  
10 obtain plasma. A 100 µL aliquot of plasma was mixed with 400 µL of methanol for protein precipitation. The supernatant was obtained and was assayed for PGE<sub>2</sub> using a radioimmunoassay kit (Amersham, RPA#530) after conversion of PGE<sub>2</sub> to its methyl oximate derivative according to the manufacturer's procedure.

15

#### B. COX-1 (Clotting-induced TxB<sub>2</sub> production)

Fresh blood was collected into vacutainers containing no anticoagulants. Aliquots of 500 µL were immediately transferred to siliconized microcentrifuge tubes preloaded with 2 µL of either DMSO  
20 or a test compound at final concentrations varying from 10nM to 30 µM. The tubes were vortexed and incubated at 37°C for 1 hour to allow blood to clot. At the end of incubation, serum was obtained by centrifugation (12,000 x g for 5 min.). A 100 µL aliquot of serum was mixed with 400 µL of methanol for protein precipitation. The  
25 supernatant was obtained and was assayed for TxB<sub>2</sub> using a enzyme immunoassay kit (Cayman, #519031) according to the manufacturer's instruction.

Compounds of the present invention are inhibitors of COX-  
30 2 and are thereby useful in the treatment of COX-2 mediated diseases as enumerated above. The activities of the compounds against cyclooxygenase may be seen in the representative results shown below. In the assay, inhibition is determined by measuring the amount of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) synthesized in the presence of A.A., COX-1

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or COX-2 and a putative inhibitor. The IC<sub>50</sub> values represent the concentration of putative inhibitor required to return PGE<sub>2</sub> synthesis to 50% of that obtained as compared to the uninhibited control.

The results for inhibition of PGE<sub>2</sub> production may  
5 be seen in Table II.

Table II

Example	HWB Cox-2 IC <sub>50</sub> (μM)	HWB Cox-1 IC <sub>50</sub> (μM)	Rat Paw Edema ED <sub>50</sub> (mg/kg)
4	1.27	>90	1.5
5	1.41	>90	1.8
6	2.42		1.4
10	<0.37		1.9
15	<0.37	>30	2.8
16	0.47		
17	0.86		
18	0.77		
20	1.95		
25	2.17	>100	2.27
26	2.11		
27	5.91		
28	2.78		
29	3.41		
30	3.36		
31	6.86		
34	3.21		
35	17.05		
40	1.18		
41	3.48		
44	21.05		
45	<0.41		6.4
46	0.88	75.5	1.89
47	1.70	38.2	

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48	4.37	>100	
49	4.71		5.56
50	2.12		10
51	1.57	66	1.53
52	17.8		
53	4.43		3.65
54	15.2		
55	8.75		
56	3.46		
57	2.75	>100	
58	2.28	>100	2.2
59	1.30		1.80
60	1.55		0.56
61			2.79
63	2.22		

The following abbreviations have the indicated meanings

	Ac	=	acetyl
5	Bn	=	benzyl
	DBU	=	diazabicyclo[5.4.0]undec-7-ene
	Et <sub>3</sub> N	=	triethylamine
	HBSS	=	Hank's balanced salt solution
	HWB	=	human whole blood
10	KHMDS	=	potassium hexamethyldisilazane
	LDA	=	lithium diisopropylamide
	MMPP	=	magnesium monoperoxyphthalate
	Ms	=	methanesulfonyl = mesyl
	MsO	=	methanesulfonate = mesylate
15	NSAID	=	non-steroidal anti-inflammatory drug
	PCC	=	pyridinium chlorochromate
	PDC	=	pyridinium dichromate
	Ph	=	phenyl
	r.t.	=	room temperature

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	rac.	=	racemic
	TFA	=	trifluoroacetic acid
	TfO	=	trifluoromethanesulfonate = triflate
	Th	=	2- or 3-thienyl
5	THF	=	tetrahydrofuran
	TLC	=	thin layer chromatography
	Ts	=	p-toluenesulfonyl = tosyl
	TsO	=	p-toluenesulfonate = tosylate
	Tz	=	1H (or 2H)-tetrazol-5-yl
10	C <sub>3</sub> H <sub>5</sub>	=	allyl
	-SO <sub>2</sub> Me	=	methyl sulfone
	-SO <sub>2</sub> NH <sub>2</sub>	=	sulfonamide

Alkyl group abbreviations

15	Me	=	methyl
	Et	=	ethyl
	n-Pr	=	normal propyl
	i-Pr	=	isopropyl
	n-Bu	=	normal butyl
20	i-Bu	=	isobutyl
	s-Bu	=	secondary butyl
	t-Bu	=	tertiary butyl
	c-Pr	=	cyclopropyl
	c-Bu	=	cyclobutyl
25	c-Pen	=	cyclopentyl
	c-Hex	=	cyclohexyl

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

30

- (i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C;

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- (ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm Hg) with a bath temperature of up to 60°C;
- 5 (iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only; (iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;
- 10 (v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data;
- 15 (vi) yields are given for illustration only;
- (vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;
- 20 (viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).
- 25

30 With regard to the preparation of certain starting materials, reference can be made to WO 95/00501, published January 5, 1995 or to US 5,474,995 issued December 12, 1995 which are hereby incorporated by reference.

#### EXAMPLE 1

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Benzoic acid 3-(4-(methylsulfonyl)phenyl)-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester

Step 1: 3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

- 5 To a solution of phenylacetic acid (27.4 g, 201 mmol) and 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (WO 9500501, Ex. 9 Step 1, hereby incorporated by reference) (60 g, 216 mmol, 1.075 eq.) in acetonitrile (630 mL) at 25 °C was added slowly Et<sub>3</sub>N (30.8 mL, 1.1 eq.). The mixture was stirred for 20 min. at r.t. and then cooled in an ice bath. DBU (60.1 mL, 3 eq.) was slowly added. After stirring for 10 20 min. in the ice bath, the reaction was complete and the mixture was acidified with 1N HCl (color changes from dark brown to yellow). Then 2.4 L of ice and water were added, stirred for a few minutes, then the precipitate was filtered and rinsed with water (giving 64 g of crude 15 wet product). The solid was dissolved in 750 mL of CH<sub>2</sub>Cl<sub>2</sub> (dried over MgSO<sub>4</sub>, filtered) and 300 g of silica gel was added. The solvent was evaporated to near dryness (silica gel a bit sticky) and the residue was applied on top of a silica gel plug (sintered glass funnel) and eluted with 10% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>, giving after evaporation of the solvent and a 20 swish in EtOAc, 36.6 g (58%) of the title compound.

Analysis      calculated for C<sub>17</sub>H<sub>14</sub>O<sub>4</sub>S  
                 C, 64.95; H, 4.49; S, 10.20  
Found:        C, 64.63; H, 4.65; S, 10.44

25

Step 2: Benzoic acid 3-(4-(methylsulfonyl)phenyl)-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester

- 30 A mixture of 0.16 g of the product from Step 1, 0.18 mL of DBU and 0.31g of benzoylperoxide in 2 mL of CH<sub>2</sub>Cl<sub>2</sub> was stirred for 3.5 h at r.t.. The reaction mixture was then diluted with 50 mL of EtOAc and washed with 50 mL of 20% NH<sub>4</sub>OAc solution. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated. The residue

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was purified by silica gel flash chromatography, eluting with 45% EtOAc/hexane to give 92 mg of the title compound as a white solid.

<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 400 MHz) δ 7.95 - 8.08 (5H, m), 7.85 (1H, s),  
5 7.79 (2H, d), 7.60 - 7.72 (2H, m), 7.41 - 7.55 (6H, m), 3.14 (3H, s).

### EXAMPLE 2

#### 10 5-Hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone

To a solution of 80 mg of the product from Step 2 in example 1 in 4 mL THF and 2 mL MeOH was added 0.5 mL of 2N aqueous NaOH solution. After stirring for 1h at r.t., the reaction  
15 mixture was treated with 5 mL of 20% aqueous NH<sub>4</sub>OAc solution and extracted with 20 mL of EtOAc. The EtOAc layer was dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel flash chromatography, eluting with 55% EtOAc/hexane to provide 10 mg of the title compound as a white solid.

20

<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 400 MHz) δ 7.98 (2H, d), 7.75 (2H, d), 7.40 (5H, m), 7.00 (1H, s), 6.76 (1H, s), 3.18 (3H, s).

### EXAMPLE 3

25

#### 5-Hydroxy-3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 400 MHz) δ 8.01 (2H, d), 7.76 (2H, d), 7.34 -  
30 7.48 (2H, m), 7.20 - 7.28 (1H, m), 7.10 (1H, s), 6.76 (1H, s), 3.17 (3H, s).

### EXAMPLE 4



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5-Hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone

A mixture of 2-bromo-1-(4-methylsulfonylphenyl)-propan-1-one (prepared using the methodology of WO 9500501, Ex. 9 Step1) (8.7 g) and phenyl acetic acid (5 g) in 150 mL of CH<sub>3</sub>CN was treated with 8.5 mL of Et<sub>3</sub>N. The reaction mixture was stirred overnight at r.t. and then 12 mL of DBU was added dropwise over 2 min. After stirring for 1 h at r.t. O<sub>2</sub> was bubbled into the mixture until it became colorless (in 45 min.). The reaction mixture was then poured into a solution of 80 mL 1N HCl and 100 mL of brine, and extracted with 500 mL of 1:1 EtOAc/hexane. The extract was dried over MgSO<sub>4</sub>, filtered and concentrated. The crude product was swished from 1:4 EtOAc/hexane (200 mL) to give 7.2 g of the title product as a white solid.

<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 400 MHz) δ 7.98 (2H, d), 7.76 (2H, d), 7.32 (5H, m), 6.86 (1H, s), 3.18 (3H, s), 1.70 (3H, s).

20

EXAMPLE 5

3-(4-Fluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 300 MHz) δ 7.98 (2H, d), 7.78 (2H, d), 7.42 (2H, dd), 7.12 (2H, t), 6.86 (1H, s), 3.16 (3H, s), 1.66 (3H, s).

25

EXAMPLE 6

3-(4-Chlorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

30

A mixture of 2-bromo-1-(4-methylsulfonylphenyl)-propan-1-one (prepared using the methodology of WO 9500501, Ex. 9 Step1) (53.8 g) and 4-chlorophenyl acetic acid (33.9 g) in 500 mL of CH<sub>3</sub>CN was treated with 28 mL of Et<sub>3</sub>N. The reaction mixture was stirred

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overnight at r.t. then diluted with 800 mL of CH<sub>3</sub>CN and cooled to 0 °C. 73 mL of DBU was added dropwise over 20 min. After stirring for 1 h at r.t. air was bubbled into the mixture and it was allowed to warm to r.t. After 4.5 h, the reaction mixture was then poured into a solution of 800 mL 1N HCl and extracted with 500 mL of EtOAc. The extract was washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The crude product was swished from ether/hexane to give 56.3 g of the title product as a white solid.

<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 400 MHz) δ 8.00 (2H, d), 7.78 (2H, d), 7.38 (3H, s), 6.90 (1H, s), 3.16 (3H, s), 1.67 (3H, s).

#### EXAMPLE 7

3-(3,4-Difluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 300 MHz) δ 8.02 (2H, d), 7.82 (2H, d), 7.25 - 7.42 (2H, m), 7.15 (1H, m), 6.92 (1H, s), 3.16 (3H, s), 1.68 (3H, s).

20

#### EXAMPLE 8

3-(3-Fluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 300 MHz) δ 8.00 (2H, d), 7.80 (2H, d), 7.30 - 7.42 (1H, m), 7.10 - 7.22 (3H, m), 6.92 (1H, s), 3.16 (3H, s), 1.70 (3H, s).

#### EXAMPLE 9

30

3-(3,5-Difluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 400 MHz) δ 8.04 (2H, d), 7.82 (2H, d), 6.95 - 7.10 (3H, m), 6.94 (1H, s), 3.18 (3H, s), 1.70 (3H, s).

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EXAMPLE 105 5-Methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone

To a solution of 5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone (Example 4) (1.0 g) in 120 mL of MeOH was added 0.1 mL of concentrated H<sub>2</sub>SO<sub>4</sub>. The mixture was  
10 heated to reflux for 3 days and then treated with 2 mL of Et<sub>3</sub>N. Methanol was removed under reduced pressure and the residue was purified by silica gel flash chromatography eluted with 4:1 toluene/EtOAc. After a swish from 2:1 hexane/EtOAc, 0.8 g of the title compound was obtained as a white solid.

15

<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 300 MHz) δ 7.98 (2H, d), 7.70 (2H, d), 7.35 - 7.65 (5H, m), 3.45 (3H, s), 3.15 (3H, s), 1.66 (3H, s).

EXAMPLE 11

20

3-(4-Chlorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 400 MHz) δ 7.98 (2H, d), 7.70 (2H, d), 7.36 - 7.46 (4H, m), 3.47 (3H, s), 3.16 (3H, s), 1.68 (3H, s).

25

EXAMPLE 1230 3-(3,4-Difluorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 300 MHz) δ 8.00 (2H, d), 7.74 (2H, d), 7.40 - 7.50 (1H, m), 7.28 - 7.40 (1H, m), 7.21 - 7.29 (1H, m), 3.47 (3H, s), 3.18 (3H, s), 1.65 (3H, s).

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EXAMPLE 13

3-(3-Fluorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

5  $^1\text{H}$  NMR ( $\text{d}_6$ -acetone, 300 MHz)  $\delta$  7.98 (2H, d), 7.71 (2H, d), 7.38-7.45 (1H, m), 7.25 - 7.29 (3H, m), 3.49 (3H, s), 3.16 (3H, s), 1.68 (3H, s).

Calc: C, 59.33; H, 4.70

Found: C, 60.12; H, 4.57

10

EXAMPLE 14

3-(3,5-Difluorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

15  $^1\text{H}$  NMR ( $\text{d}_6$ -acetone, 300 MHz)  $\delta$  8.01 (2H, d), 7.23 (2H, d), 7.05 - 7.14 (3H, m), 3.48 (3H, s), 3.16 (3H, s), 1.66 (3H, s).

EXAMPLE 15

20 3-(4-Fluorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

$^1\text{H}$  NMR ( $\text{d}_6$ -acetone, 300 MHz)  $\delta$  8.00 (2H, d), 7.72 (2H, d), 7.44 - 7.52 (2H, m), 7.12 - 7.20 (2H, m), 3.48 (3H, s), 3.17 (3H, s), 1.66 (3H, s).

25 Calc: C, 60.60; H, 4.55

Found: C, 60.55; H, 4.50

EXAMPLE 16

30

5-Ethoxy-3-(4-fluorophenyl)-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

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<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 300 MHz) δ 7.99 (2H, d), 7.72 (2H, d), 7.44 - 7.53 (2H, m), 7.12 - 7.20 (2H, m), 3.68 - 3.78 (2H, m), 3.16 (3H, s), 1.67 (3H, s), 1.28 (3H, t).

Calc: C, 61.53; H, 4.91

5 Found: C, 60.87; H, 4.90

#### EXAMPLE 17

3-(4-Fluorophenyl)-5-methyl-4-(4-(methylsulfonyl)phenyl)-5-propoxy-2-(5H)-furanone

10 <sup>1</sup>H NMR (d<sub>6</sub>-acetone, 300 MHz) δ 7.96 (2H, d), 7.70 (2H, d), 7.42 - 7.51 (2H, m), 7.10 - 7.20 (2H, m), 3.62 (2H, t), 3.16 (3H, s), 1.62 - 1.76 (2H, m), 1.66 (3H, s), 1.00 (3H, t).

Calc: C, 62.36; H, 5.23

15 Found: C, 61.86; H, 5.20

#### EXAMPLE 18

3-(4-Fluorophenyl)-5-isopropoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

20 <sup>1</sup>H NMR (d<sub>6</sub>-acetone, 300 MHz) δ 7.98 (2H, d), 7.79 (2H, d), 7.40 - 7.51 (2H, m), 7.11 - 7.19 (2H, m), 4.12 - 4.23 (1H, m), 3.15 (3H, s), 1.70 (3H, s), 1.26 (3H, d), 1.21 (3H, d).

Calc: C, 62.36; H, 5.23

25 Found: C, 62.31; H, 5.33

#### EXAMPLE 19

5-Methyl-5-methylthio-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone

30 <sup>1</sup>H NMR (d<sub>6</sub>-acetone, 400 MHz) δ 8.00 (2H, d), 7.81 (2H, d), 7.26 - 7.40 (5H, m), 3.16 (3H, s), 2.14 (3H, s), 1.80 (3H, s).

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EXAMPLE 205-Ethylthio-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone

5  $^1\text{H}$  NMR ( $\text{d}_6$ -acetone, 300 MHz)  $\delta$  8.00 (2H, d), 7.73 (2H, d), 7.28 - 7.42 (5H, m), 3.16 (3H, s), 2.56 - 2.35 (2H, m), 1.78 (3H, s), 1.28 (3H, t).

10

EXAMPLE 215-Ethyl-5-hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone

15  $^1\text{H}$  NMR ( $\text{d}_6$ -acetone, 300 MHz)  $\delta$  7.96 (2H, d), 7.80 (2H, d), 7.30-7.40 (5H, m), 6.85 (1H, s), 3.15 (3H, s), 2.0-2.15 (1H, m), 1.8-1.92 (1H, m), 0.89 (3H, t).

20

EXAMPLE 225-Ethyl-3-(3-fluorophenyl)-5-hydroxy-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

25  $^1\text{H}$  NMR ( $\text{d}_6$ -acetone, 300 MHz)  $\delta$  8.00 (2H, d), 7.80 (2H, d), 7.34-7.44 (1H, m), 7.12-7.19 (3H, m), 6.88 (1H, s), 3.15 (3H, s), 2.0-2.15 (1H, m), 1.8-1.92 (1H, m), 0.89 (3H, t).

EXAMPLE 23

30 Acetic acid, 3-(4-(methylsulfonyl)phenyl)-2-methyl-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester

$^1\text{H}$  NMR ( $\text{d}_6$ -acetone, 300 MHz)  $\delta$  8.00 (2H, d), 7.65 (2H, d), 7.40-7.52 (5H, m), 3.15 (3H, s), 2.15 (3H, s), 1.83 (3H, s)

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EXAMPLE 245-Hydroxy-5-methyl-4-((4-methylsulfonyl)phenyl)-3-(2-naphthyl)-2-(5H)-furanone

5

<sup>1</sup>H NMR (d<sub>6</sub>-acetone, 300 MHz) δ 8.08 (1H, s), 7.97 (2H, m), 7.85 (6H, m), 7.52 (2H, m), 7.30 (1H, dd), 3.14 (3H, s), 1.72 (3H, s).

Calc for C<sub>22</sub>H<sub>18</sub>O<sub>5</sub>S•1/2 H<sub>2</sub>O

C, 65.50; H, 4.75

10 Found: C, 65.24; H, 4.66

EXAMPLE 25

15 Sodium 2-(4-fluorophenyl)-3-((4-methylsulfonyl)phenyl)-4-oxo-2-pentenoate

20 To a solution of 3-(4-fluorophenyl)-5-hydroxy-5-methyl-4-((4-methylsulfonyl)phenyl)-2-(5H)-furanone (Example 5) (210 mg) in 4 mL of absolute ethanol was added 0.58 mL of a 1.00M sodium hydroxide solution. The resulting solution was concentrated to give a solid, which was subsequently dissolved in 4 mL of water. Lyophilization provided 210 mg of the title compound as a light orange solid.

25 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 300 MHz) δ 7.68 (2H, m), 7.18 (2H, m), 7.03 (2H, m), 6.91 (2H, d), 3.13 (3H, s), 2.35 (3H, s).

EXAMPLE 26

30 Calc: C, 56.84; H, 3.71  
Found: C, 56.58; H, 3.83

EXAMPLE 28

35 Calc: C, 50.34; H, 3.78  
Found: C, 50.00; H, 3.75

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EXAMPLE 29

Calc: C, 53.76; H, 3.72; N, 3.69

Found: C, 52.91; H, 3.71; N, 3.53

5

EXAMPLE 30

Calc: C, 51.08; H, 3.57

Found: C, 51.02; H, 3.74

10

EXAMPLE 31

Calc: C, 53.27; H, 3.53

Found: C, 53.32; H, 3.67

15

EXAMPLE 32

Calc: C, 58.16; H, 4.37

Found: C, 57.71; H, 4.31

20

EXAMPLE 33

Calc: C, 54.48; H, 3.56

Found: C, 54.19; H, 3.60

25

EXAMPLE 34

Calc: C, 59.12; H, 4.38; N, 4.06

Found: C, 58.40; H, 4.34; N, 3.96

30

EXAMPLE 35Calc for  $C_{19}H_{18}O_6S \cdot 1/2 H_2O$ 

C, 59.52; H, 4.99

35 Found: C, 59.65; H, 4.93



### EXAMPLE 39

**15** **EXAMPLE 40**

20 EXAMPLE 41

25 EXAMPLE 44

### EXAMPLE 45

35 Calc: C, 54.05; H, 3.63

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Found: C, 54.18; H, 3.66

EXAMPLE 46

5

m.p. 175-176°C

EXAMPLE 47

10

Calc: C, 58.44; H, 4.65

Found: C, 58.41; H, 4.72

EXAMPLE 48

15

Calc: C, 58.44; H, 4.65

Found: C, 58.41; H, 4.72

20

EXAMPLE 49

m.p. 124-125°C

25

EXAMPLE 50

m.p. 153-154°C

30

EXAMPLE 51

m.p. 123-124°C

35

EXAMPLE 52

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m.p. 131-132°C

EXAMPLE 53

5

m.p. 168-169°C

EXAMPLE 54

10

m.p. 197-198°C

EXAMPLE 55

15

Calc: C, 57.86; H, 4.09; N, 8.13

Found: C, 58.00; H, 4.21; N, 8.41

20

EXAMPLE 56

Calc: C, 53.41; H, 3.77; N, 7.50

Found: C, 53.65; H, 4.15; N, 7.51

25

EXAMPLE 57

m.p. 130-131°C

30

EXAMPLE 58

<sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 300 MHz) δ 7.64 (m, 2H), 7.17 (m, 2H), 7.05 (m, 3H), 3.12 (s, 3H), 2.35 (s, 3H).

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EXAMPLE 59

5 Sodium 2-(4-chlorophenyl)-3-((4-methylsulfonyl)phenyl)-4-oxo-2-pentenoate

To a solution of 3-(4-Chlorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone (Example 6) (50.3 g) in 200 mL of ethanol and 200 mL water was added 13.2 mL of a 10.0 M  
10 sodium hydroxide solution while cooling in an ice-bath. The resulting solution was concentrated to give a solid, which was subsequently dissolved in 200 mL of water. Lyophilization provided 52.5 g of the title compound as an off-white solid.

15 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 300 MHz) δ 7.70 (2H, m), 7.21 (2H, m), 7.17 (2H, m), 7.03 (2H, d), 3.14 (3H, s), 2.34 (3H, s).

EXAMPLE 60

20 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 400 MHz) δ 7.72 (m, 2H), 7.30 (m, 2H), 7.25 (m, 2H), 6.87 (m, 1H), 3.16 (s, 3H), 2.31 (s, 3H).

EXAMPLE 61

25 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 400 MHz) δ 7.71 (m, 2H), 7.69 (m, 2H), 7.24 (m, 2H), 6.96 (m, 2H), 3.30 (s, 3H), 2.29 (s, 3H).

EXAMPLE 63

30 <sup>1</sup>H NMR (d<sub>6</sub>-acetone, 400 MHz) δ 7.70 (m, 2H), 7.23 (m, 3H), 7.10 (m, 1H), 6.86 (m, H), 3.13 (s, 3H), 2.32 (s, 3H).

35

EXAMPLE 64

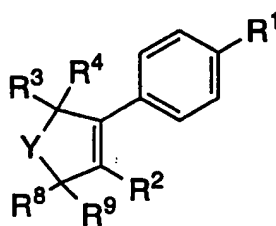
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$^1\text{H}$  NMR ( $\text{d}_6$ -acetone, 400 MHz)  $\delta$  7.65 (m, 2H), 7.16 (m, 2H), 6.93 (m, 2H), 6.13 (m, 2H), 3.15 (s, 3H), 2.38 (s, 3H).

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WHAT IS CLAIMED IS:

1. A compound of formula I



I

or a pharmaceutically acceptable salt thereof  
wherein:

Y is selected from the group consisting of

- 10 (a) C(R<sup>11</sup>)(R<sup>12</sup>),  
(b) oxygen,  
(c) sulfur,

R<sup>1</sup> is selected from the group consisting of

- 15 (a) S(O)<sub>2</sub>CH<sub>3</sub>,  
(b) S(O)<sub>2</sub>NH<sub>2</sub>,  
(c) S(O)<sub>2</sub>NHC(O)CF<sub>3</sub>,  
(d) S(O)(NH)NH<sub>2</sub>,  
(e) S(O)(NH)NHC(O)CF<sub>3</sub>,  
(f) S(O)<sub>2</sub>NHMe  
20 (g) P(O)(CH<sub>3</sub>)NH<sub>2</sub>,  
(h) P(O)(CH<sub>3</sub>)<sub>2</sub>,  
(i) C(S)NH<sub>2</sub>;

R<sup>2</sup> is selected from the group consisting of

- 25 (a) C<sub>1</sub>-10alkyl,  
(b) C<sub>3</sub>-10cycloalkyl,  
(c) C<sub>2</sub>-10alkenyl,  
(d) C<sub>2</sub>-10alkynyl,  
(e) C<sub>3</sub>-10cycloalkenyl,

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- (f) mono-, di-, tri- or tetra-substituted C<sub>3</sub>-C<sub>10</sub>cycloalkenyl wherein the substituent is selected from the group consisting of
- (1) halo,
  - (2) C<sub>1</sub>-6alkoxy,
  - (3) C<sub>1</sub>-6alkylthio,
  - (4) CN,
  - (5) CF<sub>3</sub>,
  - (6) C<sub>1</sub>-10alkyl,
  - (7) N<sub>3</sub>,
  - (8) -CO<sub>2</sub>H,
  - (9) -CO<sub>2</sub>-C<sub>1</sub>-10alkyl,
  - (10) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,
  - (11) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1</sub>-4alkyl, and
  - (12) -C<sub>1</sub>-10alkyl-CO<sub>2</sub>-R<sup>5</sup>;
  - (13) benzyloxy,
  - (14) -O-(C<sub>1</sub>-10alkyl)-CO<sub>2</sub>R<sup>5</sup>,
  - (15) -O-(C<sub>1</sub>-10alkyl)-NR<sup>5</sup>R<sup>6</sup>,
- (g) unsubstituted or mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of
- (1) halo,
  - (2) C<sub>1</sub>-10alkoxy,
  - (3) C<sub>1</sub>-10fluoroalkoxy,
  - (4) C<sub>1</sub>-10alkylthio,
  - (5) CN,
  - (6) CF<sub>3</sub>,
  - (7) C<sub>1</sub>-10alkyl,
  - (8) N<sub>3</sub>,
  - (9) -CO<sub>2</sub>H,
  - (10) -CO<sub>2</sub>-C<sub>1</sub>-10alkyl,
  - (11) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,
  - (12) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1</sub>-4alkyl, and
  - (13) -C<sub>1</sub>-6alkyl-CO<sub>2</sub>-R<sup>5</sup>;

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- (14) benzyloxy,  
(15) -O-(C<sub>1-10</sub>alkyl)-CO<sub>2</sub>R<sup>5</sup>,  
(16) -O-(C<sub>1-10</sub>alkyl)-NR<sup>5</sup>R<sup>6</sup>,
- 5 (h) unsubstituted or mono-, di- or tri-substituted heteroaryl  
wherein the heteroaryl is a monocyclic aromatic ring of 5  
atoms, said ring having one hetero atom which is S, O, or  
N, and optionally 1, 2, or 3 additional N atoms; or  
the heteroaryl is a monocyclic ring of 6 atoms, said ring  
having one hetero atom which is N, and optionally 1, 2 or 3  
10 additional N atoms, said substituents are selected from the  
group consisting of
- (1) halo,  
(2) C<sub>1-10</sub>alkyl,  
(3) C<sub>1-10</sub>alkoxy,  
15 (4) C<sub>1-10</sub>alkylthio,  
(5) CN,  
(6) CF<sub>3</sub>,  
(7) N<sub>3</sub>,  
(8) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH, and  
20 (9) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-10</sub>alkyl;
- (i) an unsubstituted or a mono- or di- substituted  
benzoheterocycle in which the heterocycle is a 5, 6, or 7-  
membered ring which may contain 1 or 2 heteroatoms  
chosen independently from O, S, or N and which may  
contain a carbonyl group or a sulfonyl group; the said  
25 substituents are selected from the group consisting of
- (1) halo,  
(2) C<sub>1-10</sub>alkyl,  
(3) C<sub>1-10</sub>alkoxy,  
30 (4) C<sub>1-10</sub>alkylthio,  
(5) CN,  
(6) CF<sub>3</sub>,  
(7) N<sub>3</sub>,  
(8) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH, and



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- (9)  $-C(R^5)(R^6)-O-C_{1-10}alkyl$ ;
- (j) a heterocycloalkyl group of 5, 6 or 7 members which contains 1 or 2 heteroatoms chosen from O, S, or N and optionally contains a carbonyl group or a sulfonyl group.
- 5 (k) an unsubstituted or a mono- or di- substituted benzocarbocycle in which the carbocycle is a 5, 6, or 7-membered ring which optionally contains a carbonyl group, the said substituents are selected from the group consisting of
- 10 (1) halo,
- (2)  $C_{1-10}alkyl$ ,
- (3)  $C_{1-10}alkoxy$ ,
- (4)  $C_{1-10}alkylthio$ ,
- (5) CN,
- 15 (6)  $CF_3$ ,
- (7)  $N_3$ ,
- (8)  $-C(R^5)(R^6)-OH$ , and
- (9)  $-C(R^5)(R^6)-O-C_{1-10}alkyl$ ;
- $R^3$  is hydrogen,  $C_{1-10}alkyl$ ,  $CH_2OR^7$ , CN,  $CH_2CN$ , or  $C_{1-6}fluoroalkyl$ , F,  $CONR^7_2$ , unsubstituted or mono- or di-substituted phenyl, unsubstituted or mono or di-substituted benzyl, unsubstituted or mono- or di-substituted heteroaryl, unsubstituted or mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of
- 25 (1) halo,
- (2)  $C_{1-10}alkyl$ ,
- (3)  $C_{1-10}alkoxy$ ,
- (4)  $C_{1-10}alkylthio$ ,
- (5) CN,
- 30 (6)  $CF_3$ ,
- (7)  $N_3$ ,
- (8)  $-C(R^5)(R^6)-OH$ , and
- (9)  $-C(R^5)(R^6)-O-C_{1-10}alkyl$ ;

 $R^4$  is

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- 5 (a) C<sub>1-10</sub>alkoxy,  
 (b) C<sub>1-10</sub>fluoroalkoxy,  
 (c) C<sub>1-10</sub>alkylthio,  
 (d) -OH,  
 (e) -OCOR<sup>7</sup>,  
 (f) -SH,  
 (g) -SCOR<sup>7</sup>,  
 (h) -OCO<sub>2</sub>R<sup>8</sup>,  
 (i) -SCO<sub>2</sub>R<sup>8</sup>,  
 10 (j) OCONR<sup>7</sup><sub>2</sub>,  
 (k) SCONR<sup>7</sup><sub>2</sub>,  
 (l) C<sub>3-10</sub>cycloalkoxy, and  
 (m) C<sub>3-10</sub>cycloalkylthio;
- 15 each R<sup>5</sup> or R<sup>6</sup> is independently selected from the group consisting of  
 (a) hydrogen, and  
 (b) C<sub>1-10</sub>alkyl,  
 or R<sup>5</sup> and R<sup>6</sup> together with the carbon to which they are attached  
 form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7  
 20 atoms;
- each R<sup>7</sup> is independently selected from the group consisting of  
 (a) hydrogen and  
 (b) R<sup>8</sup>;
- 25 each R<sup>8</sup> is independently selected from the group consisting of  
 (a) C<sub>1-10</sub>alkyl,  
 (b) phenyl or monosubstituted phenyl wherein the substituents  
 may be halo, C<sub>1-10</sub>alkyl, C<sub>1-10</sub>alkoxy, C<sub>1-10</sub>alkylthio,  
 CN, or CF<sub>3</sub>,  
 (c) benzyl or monosubstituted benzyl wherein the substituents  
 30 may be halo, C<sub>1-10</sub>alkyl, C<sub>1-10</sub>alkoxy, C<sub>1-10</sub>alkylthio,  
 CN, or CF<sub>3</sub>, and  
 (d) C<sub>3-10</sub>cycloalkyl
- R<sup>9</sup> and R<sup>10</sup> are independently selected from the group consisting of:  
 (a) hydrogen,

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(b) C<sub>1-10</sub>alkyl,(c) C<sub>3-10</sub>cycloalkyl, orR<sup>9</sup> and R<sup>10</sup> together form a double bonded O or S;R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of:

5

(a) hydrogen ,

(b) unsubstituted or mono- or di-substituted phenyl or unsubstituted or mono- or di-substituted benzyl or unsubstituted or mono- or di-substituted heteroaryl or mono- or di-substituted heteroarylmethyl, said substituents are selected from the group consisting of:

10

(1) halo,

(2) C<sub>1-10</sub>alkyl,(3) C<sub>1-10</sub>alkoxy,(4) C<sub>1-10</sub>alkylthio,

15

(5) CN,

(6) CF<sub>3</sub>,(7) N<sub>3</sub>,(8) -C(R<sup>13</sup>)(R<sup>14</sup>)-OH, and(9) -C(R<sup>13</sup>)(R<sup>14</sup>)-O-C<sub>1-10</sub>alkyl, or

20

(c) C<sub>1-10</sub>alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, C<sub>1-10</sub>fluoroalkyl, F or CONR<sup>7</sup><sub>2</sub>, orR<sup>11</sup> and R<sup>12</sup> together with the carbon to which they are attached form a carbonyl or a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

25

R<sup>13</sup> and R<sup>14</sup> are independently selected from the group consisting of:

(a) hydrogen,

(b) C<sub>1-10</sub>alkyl, orR<sup>13</sup> and R<sup>14</sup> together with the carbon to which they are attached form a carbonyl, -C(=S)-, or a saturated monocyclic carbon ring of 3, 4, 5, 6, or 7 atoms.

30

2. A compound according to Claim 1

wherein:

35

Y is selected from the group consisting of

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- (a) C(R<sup>11</sup>)(R<sup>12</sup>),
- (b) oxygen,
- (c) sulfur,

R<sup>1</sup> is selected from the group consisting of

- 5 (a) S(O)<sub>2</sub>CH<sub>3</sub>,
- (b) S(O)<sub>2</sub>NH<sub>2</sub>,
- (c) S(O)<sub>2</sub>NHC(O)CF<sub>3</sub>,
- (d) S(O)(NH)NH<sub>2</sub>,
- (e) S(O)(NH)NHC(O)CF<sub>3</sub>,

10

R<sup>2</sup> is selected from the group consisting of

- (a) C<sub>3</sub>-10cycloalkyl,
- (b) C<sub>3</sub>-8cycloalkenyl,
- (c) mono-, di- or tri- -substituted C<sub>3</sub>-C<sub>8</sub>cycloalkenyl wherein  
15 the substituent is selected from the group consisting of
  - (1) halo,
  - (2) C<sub>1</sub>-6alkoxy,
  - (3) C<sub>1</sub>-6alkylthio,
  - (4) CN,
  - 20 (5) CF<sub>3</sub>,
  - (6) C<sub>1</sub>-6alkyl,
  - (7) N<sub>3</sub>,
  - (8) -CO<sub>2</sub>H,
  - (9) -CO<sub>2</sub>-C<sub>1</sub>-10alkyl,
  - 25 (10) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,
  - (11) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1</sub>-4alkyl, and
  - (12) -C<sub>1</sub>-6alkyl-CO<sub>2</sub>-R<sup>5</sup>;
  - (13) -O-(C<sub>1</sub>-6alkyl)-CO<sub>2</sub>R<sup>5</sup>,
- (d) unsubstituted or mono-, di- or tri-substituted phenyl or  
30 naphthyl wherein the substituent is selected from the group consisting of
  - (1) halo,
  - (2) C<sub>1</sub>-6alkoxy,
  - (3) C<sub>1</sub>-6alkylthio,

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- 5 (4) CN,  
(5) CF<sub>3</sub>,  
(6) C<sub>1-6</sub>alkyl,  
(7) N<sub>3</sub>,  
(8) -CO<sub>2</sub>H,  
(9) -CO<sub>2</sub>-C<sub>1-6</sub>alkyl,  
(10) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,  
(11) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-4</sub>alkyl, and  
(12) -C<sub>1-6</sub>alkyl-CO<sub>2</sub>-R<sup>5</sup>;  
10 (13) -O-(C<sub>1-6</sub>alkyl)-CO<sub>2</sub>R<sup>5</sup>,
- (e) unsubstituted or mono-, di- or tri-substituted heteroaryl  
wherein the heteroaryl is a monocyclic aromatic ring of 5  
atoms, said ring having one hetero atom which is S, O, or  
N, and optionally 1, 2, or 3 additional N atoms; or  
15 the heteroaryl is a monocyclic ring of 6 atoms, said ring  
having one hetero atom which is N, and optionally 1, 2 or 3  
additional N atoms, said substituents are selected from the  
group consisting of
- 20 (1) halo,  
(2) C<sub>1-6</sub>alkyl,  
(3) C<sub>1-6</sub>alkoxy,  
(4) C<sub>1-6</sub>alkylthio,  
(5) CN,  
(6) CF<sub>3</sub>,  
25 (7) N<sub>3</sub>,  
(8) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH, and  
(9) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-6</sub>alkyl;
- (f) an unsubstituted or a mono- or di- substituted  
benzoheterocycle in which the heterocycle is a 5, 6, or 7-  
30 membered ring which may contain 1 or 2 heteroatoms  
chosen independently from O, S, or N and which may  
contain a carbonyl group or a sulfonyl group; the said  
substituents are selected from the group consisting of  
(1) halo,

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- 5 (2) C<sub>1-6</sub>alkyl,  
 (3) C<sub>1-6</sub>alkoxy,  
 (4) C<sub>1-6</sub>alkylthio,  
 (5) CN,  
 (6) CF<sub>3</sub>,  
 (7) N<sub>3</sub>,  
 (8) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH, and  
 (9) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-10</sub>alkyl;
- 10 (g) a heterocycloalkyl group of 5, 6 or 7 members which contains 1 or 2 heteroatoms chosen from O, S, or N and optionally contains a carbonyl group or a sulfonyl group.
- (h) an unsubstituted or a mono- or di- substituted benzocarbocycle in which the carbocycle is a 5, 6, or 7-membered ring which optionally contains a carbonyl group,  
 15 the said substituents are selected from the group consisting of
- (1) halo,  
 (2) C<sub>1-6</sub>alkyl,  
 (3) C<sub>1-6</sub>alkoxy,  
 20 (4) C<sub>1-6</sub>alkylthio,  
 (5) CN,  
 (6) CF<sub>3</sub>,  
 (7) N<sub>3</sub>,  
 (8) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH, and  
 25 (9) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-6</sub>alkyl;
- R<sup>3</sup> is hydrogen, C<sub>1-6</sub>alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, or C<sub>1-6</sub>fluoroalkyl, F, CONR<sup>7</sup><sub>2</sub>, unsubstituted or mono- or di-substituted phenyl, unsubstituted or mono or di-substituted benzyl, unsubstituted or mono- or di-substituted heteroaryl, unsubstituted or mono or di-substituted  
 30 heteroarylmethyl, wherein the substituents are selected from the group consisting of
- (1) halo,  
 (2) C<sub>1-6</sub>alkyl,  
 (3) C<sub>1-6</sub>alkoxy,

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- 5
- (4) C<sub>1</sub>-6alkylthio,
  - (5) CN,
  - (6) CF<sub>3</sub>,
  - (7) N<sub>3</sub>,
  - (8) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH, and
  - (9) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1</sub>-6alkyl;

R<sup>4</sup> is

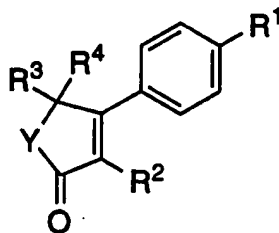
- 10
- (a) C<sub>1</sub>-6alkoxy,
  - (b) C<sub>1</sub>-6alkylthio,
  - (c) -OH,
  - (d) -OCOR<sup>7</sup>,
  - (e) -SH,
  - (f) -SCOR<sup>7</sup>,
  - (g) -OCO<sub>2</sub>R<sup>8</sup>,
  - 15 (h) -SCO<sub>2</sub>R<sup>8</sup>,
  - (i) OCONR<sup>7</sup><sub>2</sub>, and
  - (j) SCONR<sup>7</sup><sub>2</sub>;

- 20 each R<sup>5</sup> or R<sup>6</sup> is independently selected from the group consisting of
- (a) hydrogen, and
  - (b) C<sub>1</sub>-6alkyl,
- or R<sup>5</sup> and R<sup>6</sup> together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;
- 25 each R<sup>7</sup> is independently selected from the group consisting of
- (a) hydrogen and
  - (b) R<sup>8</sup>;
- each R<sup>8</sup> is independently selected from the group consisting of
- (a) C<sub>1</sub>-6alkyl,
  - 30 (b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C<sub>1</sub>-6alkyl, C<sub>1</sub>-6alkoxy, C<sub>1</sub>-6alkylthio, CN, or CF<sub>3</sub>,

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- (c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C<sub>1</sub>-6alkyl, C<sub>1</sub>-6alkoxy, C<sub>1</sub>-6alkylthio, CN, or CF<sub>3</sub>, and
- (d) C<sub>3</sub>-6cycloalkyl
- 5 R<sup>9</sup> and R<sup>10</sup> are independently selected from the group consisting of:
- (a) hydrogen,
- (b) C<sub>1</sub>-6alkyl,
- (c) C<sub>3</sub>-6cycloalkyl, or
- R<sup>9</sup> and R<sup>10</sup> together form a double bonded O;
- 10 R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of:
- (a) hydrogen ,
- (b) C<sub>1</sub>-10alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, C<sub>1</sub>-6fluoroalkyl, F or CONR<sup>7</sup><sub>2</sub>; or
- R<sup>11</sup> and R<sup>12</sup> together with the carbon to which they are attached
- 15 form a carbonyl or a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;
- R<sup>13</sup> and R<sup>14</sup> are independently selected from the group consisting of:
- (a) hydrogen,
- (b) C<sub>1</sub>-6alkyl, or
- 20 R<sup>13</sup> and R<sup>14</sup> together with the carbon to which they are attached form a carbonyl or a saturated monocyclic carbon ring of 3, 4, 5, 6, or 7 atoms.

25 3. A compound according to Claim 2 of formula Ia



Ia

or a pharmaceutically acceptable salt thereof



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wherein:

Y is selected from the group consisting of

- (a) C(R<sup>11</sup>)(R<sup>12</sup>),
- (b) oxygen,
- 5 (c) sulfur,

R<sup>1</sup> is selected from the group consisting of

- (a) S(O)<sub>2</sub>CH<sub>3</sub>,
- (b) S(O)<sub>2</sub>NH<sub>2</sub>,
- (c) S(O)<sub>2</sub>NHC(O)CF<sub>3</sub>,
- 10 (d) S(O)(NH)NH<sub>2</sub>,
- (e) S(O)(NH)NHC(O)CF<sub>3</sub>,

R<sup>2</sup> is selected from the group consisting of

- (a) C<sub>3-6</sub>cycloalkyl,
- 15 (b) mono- or di- substituted C<sub>3-6</sub>cycloalkenyl wherein the substituent is selected from the group consisting of
  - (1) halo,
  - (2) C<sub>1-4</sub>alkoxy,
  - (3) C<sub>1-4</sub>alkylthio,
  - 20 (4) CN,
  - (5) CF<sub>3</sub>,
  - (6) C<sub>1-6</sub>alkyl,
  - (7) N<sub>3</sub>,
  - (8) -CO<sub>2</sub>H,
  - 25 (9) -CO<sub>2</sub>-C<sub>1-6</sub>alkyl,
  - (10) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,
  - (11) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-4</sub>alkyl,
- (c) unsubstituted or mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of
  - 30 (1) halo,
  - (2) C<sub>1-4</sub>alkoxy,
  - (3) C<sub>1-4</sub>alkylthio,
  - (4) CN,

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- 5
- (5) CF<sub>3</sub>,  
(6) C<sub>1-6</sub>alkyl,  
(7) N<sub>3</sub>,  
(8) -CO<sub>2</sub>H,  
(9) -CO<sub>2</sub>-C<sub>1-4</sub>alkyl,  
(10) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,  
(11) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-4</sub>alkyl, and  
(12) -C<sub>1-4</sub>alkyl-CO<sub>2</sub>-R<sup>5</sup>;  
(13) -O-(C<sub>1-4</sub>alkyl)-CO<sub>2</sub>R<sup>5</sup>,
- 10 (d) unsubstituted or mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or
- 15 the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2 or 3 additional N atoms, said substituents are selected from the group consisting of
- 20 (1) halo,  
(2) C<sub>1-4</sub>alkyl,  
(3) C<sub>1-4</sub>alkoxy,  
(4) C<sub>1-4</sub>alkylthio,  
(5) CN,  
(6) CF<sub>3</sub>,  
(7) N<sub>3</sub>,
- 25 (8) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH, and  
(9) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-4</sub>alkyl;
- (e) an unsubstituted or a mono- or di- substituted
- 30 benzoheterocycle in which the heterocycle is a 5, 6, or 7-membered ring which may contain 1 or 2 heteroatoms chosen independently from O, S, or N and which may contain a carbonyl group or a sulfonyl group; the said substituents are selected from the group consisting of
- (1) halo,  
(2) C<sub>1-4</sub>alkyl,

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- 5 (3) C<sub>1-4</sub>alkoxy,  
(4) C<sub>1-4</sub>alkylthio,  
(5) CN,  
(6) CF<sub>3</sub>,  
(7) N<sub>3</sub>,  
(8) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH, and  
(9) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-4</sub>alkyl;
- 10 (f) a heterocycloalkyl group of 5, 6 or 7 members which  
contains 1 or 2 heteroatoms chosen from O, S, or N and  
optionally contains a carbonyl group or a sulfonyl group.
- (g) an unsubstituted or a mono- or di- substituted  
15 benzocarbocycle in which the carbocycle is a 5, 6, or 7-  
membered ring which optionally contains a carbonyl group,  
the said substituents are selected from the group consisting  
of
- 20 (1) halo,  
(2) C<sub>1-4</sub>alkyl,  
(3) C<sub>1-4</sub>alkoxy,  
(4) C<sub>1-4</sub>alkylthio,  
(5) CN,  
(6) CF<sub>3</sub>,  
(7) N<sub>3</sub>,  
(8) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH, and  
(9) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-4</sub>alkyl;
- 25 R<sup>3</sup> is hydrogen, C<sub>1-4</sub>alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, or C<sub>1-4</sub>fluoroalkyl,  
F, CONR<sup>7</sup><sub>2</sub>, unsubstituted or mono- or di-substituted phenyl,  
unsubstituted or mono or di-substituted benzyl, unsubstituted or mono-  
or di-substituted heteroaryl, unsubstituted or mono or di-substituted  
heteroarylmethyl, wherein the substituents are selected from the group  
30 consisting of
- (1) halo,  
(2) C<sub>1-4</sub>alkyl,  
(3) C<sub>1-4</sub>alkoxy,  
(4) C<sub>1-4</sub>alkylthio,

- 5
- R<sup>4</sup> is
- (5) CN,  
(6) CF<sub>3</sub>,  
(7) N<sub>3</sub>,  
(8) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH, and  
(9) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-4</sub>alkyl;
- 10
- (a) C<sub>1-4</sub>alkoxy,  
(b) C<sub>1-4</sub>alkylthio,  
(c) -OH,  
(d) -OCOR<sup>7</sup>,  
(e) -SH,  
(f) -SCOR<sup>7</sup>,  
(g) -OCO<sub>2</sub>R<sup>8</sup>,  
(h) -SCO<sub>2</sub>R<sup>8</sup>,
- 15
- (i) OCONR<sup>7</sup><sub>2</sub>, and  
(j) SCONR<sup>7</sup><sub>2</sub>;

each  $R^5$  or  $R^6$  is independently selected from the group consisting of

- 20 (a) hydrogen, and  
(b) C<sub>1-4</sub>alkyl,

each  $R^7$  is independently selected from the group consisting of

- (a) hydrogen and  
(b) R<sup>8</sup>;

each  $R^8$  is independently selected from the group consisting of

- 25 (a) C1-6alkyl,  
(b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C1-4alkyl, C1-4alkoxy, C1-4alkylthio, CN, or CF<sub>3</sub>,

- (c) benzyl or monosubstituted benzyl wherein the substituents  
30 may be halo, C<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkoxy, C<sub>1</sub>-4alkylthio, CN, or CF<sub>3</sub>;

**R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of:**

- (a) hydrogen ,  
(b) C<sub>1</sub>-4alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, C<sub>1</sub>-4fluoroalkyl, F or CONR<sup>7</sup><sub>2</sub>;

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R<sup>13</sup> and R<sup>14</sup> are independently selected from the group consisting of:

- (a) hydrogen,
- (b) C<sub>1-4</sub>alkyl.

5

4. A compound according to Claim 3

wherein:

Y is selected from the group consisting of

- (a) C(R<sup>11</sup>)(R<sup>12</sup>),
- (b) oxygen,
- 10 (c) sulfur,

R<sup>1</sup> is selected from the group consisting of

- (a) S(O)<sub>2</sub>CH<sub>3</sub>,
- (b) S(O)<sub>2</sub>NH<sub>2</sub>,
- (c) S(O)<sub>2</sub>NHC(O)CF<sub>3</sub>,
- 15 (d) S(O)(NH)NH<sub>2</sub>,
- (e) S(O)(NH)NHC(O)CF<sub>3</sub>,

R<sup>2</sup> is selected from the group consisting of

- (a) C<sub>3-6</sub>cycloalkyl,
- (b) unsubstituted or mono-, di- or tri-substituted phenyl or
- 20 naphthyl wherein the substituent is selected from the group consisting of
- (1) halo,
- (2) C<sub>1-6</sub>alkoxy,
- (3) C<sub>1-6</sub>alkylthio,
- 25 (4) CN,
- (5) CF<sub>3</sub>,
- (6) C<sub>1-6</sub>alkyl,
- (7) N<sub>3</sub>,
- (8) -CO<sub>2</sub>H,
- 30 (9) -CO<sub>2</sub>-C<sub>1-6</sub>alkyl,
- (10) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,
- (11) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-4</sub>alkyl, and
- (12) -C<sub>1-6</sub>alkyl-CO<sub>2</sub>-R<sup>5</sup>;
- (13) -O-(C<sub>1-6</sub>alkyl)-CO<sub>2</sub>R<sup>5</sup>,
- 35

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$R^3$  is hydrogen,  $C_{1-4}$ alkyl,  $CH_2OR^7$ , CN,  $CH_2CN$ , or  $C_{1-4}$ fluoroalkyl, F,  $CONR^7_2$ , unsubstituted or mono- or di-substituted phenyl, unsubstituted or mono or di-substituted benzyl, wherein the substituents are selected from the group consisting of

- 5 (1) halo,
- (2)  $C_{1-4}$ alkyl,
- (3)  $C_{1-4}$ alkoxy,
- (4)  $C_{1-4}$ alkylthio,
- (5) CN,
- 10 (6)  $CF_3$ ,
- (7)  $N_3$ ,
- (8)  $-C(R^5)(R^6)-OH$ , and
- (9)  $-C(R^5)(R^6)-O-C_{1-10}$ alkyl;

$R^4$  is

- 15 (a)  $C_{1-4}$ alkoxy,
- (b)  $C_{1-4}$ alkylthio,
- (c)  $-OH$ ,
- (d)  $-OCOR^7$ ,
- (e)  $-SH$ ,
- 20 (f)  $-SCOR^7$ ,
- (g)  $-OCO_2R^8$ ,
- (h)  $-SCO_2R^8$ ,
- (i)  $ONR^7_2$ , and
- (j)  $SONR^7_2$ ;

25 each  $R^5$  or  $R^6$  is independently selected from the group consisting of

- (a) hydrogen, and
- (b)  $C_{1-4}$ alkyl,

each  $R^7$  is independently selected from the group consisting of

- 30 (a) hydrogen and
- (b)  $R^8$ ;

each  $R^8$  is independently selected from the group consisting of

- (a)  $C_{1-4}$ alkyl,

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- (b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkoxy, C<sub>1</sub>-4alkylthio, CN, or CF<sub>3</sub>,  
(c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkoxy, C<sub>1</sub>-4alkylthio, CN, or CF<sub>3</sub>,

R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of:

- (a) hydrogen ,  
(b) C<sub>1</sub>-4alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, C<sub>1</sub>-4fluoroalkyl, F or CONR<sup>7</sup><sub>2</sub>; or

R<sup>11</sup> and R<sup>12</sup> together with the carbon to which they are attached form a carbonyl or a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R<sup>13</sup> and R<sup>14</sup> are independently selected from the group consisting of:

- (a) hydrogen,  
(b) C<sub>1</sub>-4alkyl, or

R<sup>13</sup> and R<sup>14</sup> together with the carbon to which they are attached form a carbonyl.

5. A compound according to Claim 4

wherein:

Y is selected from the group consisting of

- (a) C(R<sup>11</sup>)(R<sup>12</sup>),  
(b) oxygen,  
(c) sulfur,

R<sup>1</sup> is selected from the group consisting of

- (a) S(O)<sub>2</sub>CH<sub>3</sub>,  
(b) S(O)<sub>2</sub>NH<sub>2</sub>,  
(c) S(O)<sub>2</sub>NHC(O)CF<sub>3</sub>,  
(d) S(O)(NH)NH<sub>2</sub>,  
(e) S(O)(NH)NHC(O)CF<sub>3</sub>;

R<sup>2</sup> is selected from the group consisting of

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unsubstituted or mono-, di- or tri-substituted phenyl  
wherein the substituent is selected from the group  
consisting of

- (1) halo,
- (2) C<sub>1</sub>-6alkoxy,
- (3) C<sub>1</sub>-6alkylthio,
- (4) CN,
- (5) CF<sub>3</sub>,
- (6) C<sub>1</sub>-6alkyl,
- (7) N<sub>3</sub>,
- (8) -CO<sub>2</sub>H,
- (9) -CO<sub>2</sub>-C<sub>1</sub>-6alkyl,
- (10) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,
- (11) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1</sub>-4alkyl;

R<sup>3</sup> is hydrogen, C<sub>1</sub>-4alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, or C<sub>1</sub>-4fluoroalkyl,  
F, CONR<sup>7</sup><sub>2</sub>, unsubstituted or mono- or di-substituted phenyl, wherein  
the substituents are selected from the group consisting of

- (1) halo,
- (2) C<sub>1</sub>-4alkyl,
- (3) C<sub>1</sub>-4alkoxy,
- (4) C<sub>1</sub>-4alkylthio,
- (5) CF<sub>3</sub>,
- (6) N<sub>3</sub>,
- (7) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH, and

R<sup>4</sup> is

- (a) C<sub>1</sub>-4alkoxy,
- (b) C<sub>1</sub>-4alkylthio,
- (c) -OH,
- (d) -OCOR<sup>7</sup>,
- (e) -SH,
- (f) -SCOR<sup>7</sup>,
- (g) -OCO<sub>2</sub>R<sup>8</sup>,
- (h) -SCO<sub>2</sub>R<sup>8</sup>,
- (i) OCONR<sup>7</sup><sub>2</sub>, and



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(j)  $\text{SCONR}^7_2$ ;each  $\text{R}^5$  or  $\text{R}^6$  is independently selected from the group consisting of

- (a) hydrogen, and
- (b) C1-4alkyl,

5 each  $\text{R}^7$  is independently selected from the group consisting of

- (a) hydrogen and
- (b)  $\text{R}^8$ ;

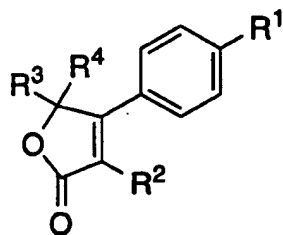
each  $\text{R}^8$  is independently selected from the group consisting of

- (a) C1-4alkyl,
- 10 (b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C1-4alkyl, C1-4alkoxy, C1-4alkylthio, CN, or  $\text{CF}_3$ ,

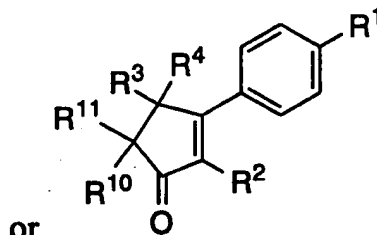
 $\text{R}^{11}$  and  $\text{R}^{12}$  are independently selected from the group consisting of:

- (a) hydrogen ,
- 15 (b) C1-4alkyl,  $\text{CH}_2\text{OR}^7$ , CN,  $\text{CH}_2\text{CN}$ , C1-4fluoroalkyl, F or  $\text{CONR}^7_2$ .

6. A compound according to Claim 5 of formula Ib or

Ic  
20

Ib



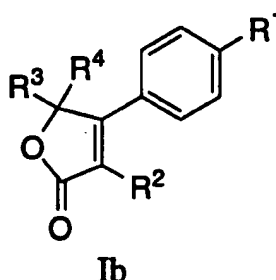
Ic

or a pharmaceutically acceptable salt thereof.

25

7. A compound according to Claim 6 of formula Ib

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wherein:

R<sup>1</sup> is selected from the group consisting of

- 5           (a) S(O)<sub>2</sub>CH<sub>3</sub>,  
              (b) S(O)<sub>2</sub>NH<sub>2</sub>,  
              (c) S(O)<sub>2</sub>NHC(O)CF<sub>3</sub>,  
              (d) S(O)(NH)NH<sub>2</sub>;

R<sup>2</sup> is selected from the group consisting of

10           unsubstituted or mono-, di- or tri-substituted phenyl  
              wherein the substituent is selected from the group  
              consisting of

- 15           (1) halo,  
              (2) C<sub>1</sub>-4alkoxy,  
              (3) C<sub>1</sub>-4alkylthio,  
              (4) CN,  
              (5) CF<sub>3</sub>,  
              (6) C<sub>1</sub>-4alkyl,  
              (7) N<sub>3</sub>,  
              (8) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,

20           R<sup>3</sup> is hydrogen, C<sub>1</sub>-4alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, or C<sub>1</sub>-4fluoroalkyl,  
              F, CONR<sup>7</sup><sub>2</sub>;

R<sup>4</sup> is

- 25           (a) C<sub>1</sub>-4alkoxy,  
              (b) C<sub>1</sub>-4alkylthio,  
              (c) -OH,  
              (d) -OCOR<sup>7</sup>,  
              (e) -SH,  
              (f) -SCOR<sup>7</sup>,  
              (g) -OCO<sub>2</sub>R<sup>8</sup>,
- 30

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- (h)  $-\text{SCO}_2\text{R}^8$ ,
- (i)  $\text{OCONR}^{72}$ , and
- (j)  $\text{SCONR}^{72}$ ;

each  $\text{R}^5$  or  $\text{R}^6$  is independently selected from the group consisting of

- 5 (a) hydrogen, and
- (b)  $\text{C}_{1-4}$ alkyl,

each  $\text{R}^7$  is independently selected from the group consisting of

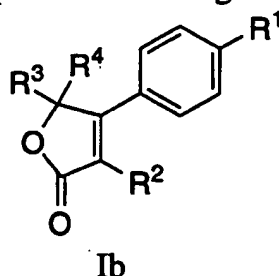
- (a) hydrogen and
- (b)  $\text{R}^8$ ;

10 each  $\text{R}^8$  is independently selected from the group consisting of

- (a)  $\text{C}_{1-4}$ alkyl,
- (b) phenyl or monosubstituted phenyl wherein the substituents may be halo,  $\text{C}_{1-4}$ alkyl,  $\text{C}_{1-4}$ alkoxy,  $\text{C}_{1-4}$ alkylthio, CN, or  $\text{CF}_3$ .

15

8. A compound according to Claim 7 of formula Ib



wherein:

20  $\text{R}^1$  is selected from the group consisting of

- (a)  $\text{S}(\text{O})_2\text{CH}_3$ ,
- (b)  $\text{S}(\text{O})_2\text{NH}_2$ ,

$\text{R}^2$  is selected from the group consisting of

unsubstituted or mono-, di- or tri-substituted phenyl  
 wherein the substituent is selected from the group  
 consisting of

25

- (1) halo,
- (2)  $\text{C}_{1-3}$ alkoxy,
- (3)  $\text{CF}_3$ ,
- (4)  $\text{C}_{1-3}$ alkyl,

30

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$R^3$  is hydrogen, C<sub>1</sub>-3alkyl, CH<sub>2</sub>OR<sup>7</sup>, C<sub>1</sub>-4fluoroalkyl, F, CONR<sup>7</sup><sub>2</sub>;

$R^4$  is

- (a) C<sub>1</sub>-3alkoxy,
- (b) C<sub>1</sub>-3alkylthio,
- 5 (c) -OH,
- (d) -OCOR<sup>7</sup>,
- (e) -SCOR<sup>7</sup>,
- (f) OCONR<sup>7</sup><sub>2</sub>, and
- (g) SCONR<sup>7</sup><sub>2</sub>;

10 each  $R^5$  or  $R^6$  is independently selected from the group consisting of

- (a) hydrogen, and
- (b) C<sub>1</sub>-3alkyl,

each  $R^7$  is independently selected from the group consisting of

- (a) hydrogen and
  - 15 (b)  $R^8$ ;
- each  $R^8$  is C<sub>1</sub>-3alkyl.

9. A compound according to Claim 3

wherein:

20 Y is selected from the group consisting of

- (a) C(R<sup>11</sup>)(R<sup>12</sup>),
- (b) oxygen,
- (c) sulfur,

$R^1$  is selected from the group consisting of

- 25 (a) S(O)<sub>2</sub>CH<sub>3</sub>,
- (b) S(O)<sub>2</sub>NH<sub>2</sub>,
- (c) S(O)<sub>2</sub>NHC(O)CF<sub>3</sub>,
- (d) S(O)(NH)NH<sub>2</sub>,
- (e) S(O)(NH)NHC(O)CF<sub>3</sub>,
- 30 (f) P(O)(CH<sub>3</sub>)NH<sub>2</sub>,

$R^2$  is selected from the group consisting of

- (a) mono- or di-substituted heteroaryl selected from the group consisting of

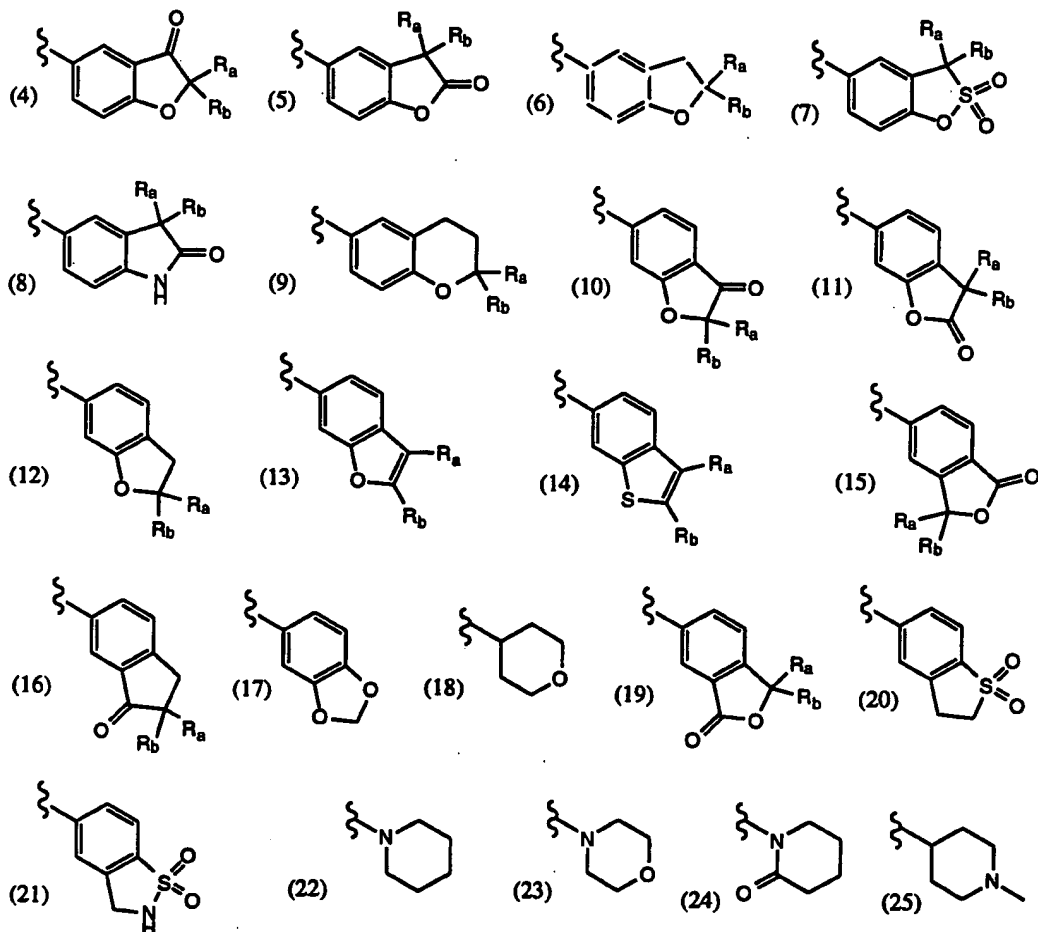
- 91 -

- 5 (1) furanyl,  
(2) diaziny, triaziny and tetraziny,  
(3) imidazolyl,  
(4) isooxazolyl,  
(5) isothiazolyl,  
(6) oxadiazolyl,  
(7) oxazolyl,  
(8) pyrazolyl,  
(9) pyrrolyl,  
10 (10) thiadiazolyl,  
(11) thiazolyl,  
(12) thienyl,  
(13) triazolyl, and  
(14) tetrazolyl,  
15 wherein said substituents are selected from the group consisting of  
(1) hydrogen,  
(2) fluoro, chloro, bromo and iodo,  
(3) C<sub>1</sub>-6alkyl,  
(4) C<sub>1</sub>-6alkoxy,  
20 (5) C<sub>1</sub>-6alkylthio,  
(6) CN,  
(7) CF<sub>3</sub>,  
(8) N<sub>3</sub>,  
(9) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH, and  
25 (10) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1</sub>-4alkyl;  
(b) a mono- or di-substituted benzoheterocycle,  
benzocarbocycle or heterocycloalkyl selected from the  
group consisting of  
30 (1) 2-indolyl,  
(2) 3-indolyl,  
(3) 1-methyl-5-indolyl  
(4) 2-benzofuranyl,  
(5) 3-benzofuranyl,  
(6) 5-benzofuranyl,

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5

- (7) 6-benzofuranyl,  
 (8) 2-benzothienyl,  
 (9) 3-benzothienyl,  
 (10) 5-benzothienyl,  
 (11) 6-benzothienyl,



in which the substituents comprise  $R_a$  and  $R_b$  and said substituents are selected from halo, -OH,  $CF_3$ , C1-3alkoxy,

C1-3alkylthio, and C1-3alkyl;

10

$R^3$  is hydrogen, C1-6alkyl,  $CH_2OR^7$ , CN,  $CH_2CN$ , or C1-6fluoroalkyl, F,  $CONR^7_2$ , unsubstituted or mono- or di-substituted phenyl, unsubstituted or mono or di-substituted benzyl, unsubstituted or mono- or di-substituted heteroaryl, unsubstituted or mono or di-substituted

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heteroarylmethyl, wherein the substituents are selected from the group consisting of

- 5 (1) halo,  
 (2) C<sub>1-4</sub>alkyl,  
 (3) C<sub>1-4</sub>alkoxy,  
 (4) C<sub>1-4</sub>alkylthio,  
 (5) CN,  
 (6) CF<sub>3</sub>,  
 (7) N<sub>3</sub>,  
 10 (8) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH, and  
 (9) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1-10</sub>alkyl;

R<sup>4</sup> is

- 15 (a) C<sub>1-4</sub>alkoxy,  
 (b) C<sub>1-4</sub>alkylthio,  
 (c) -OH,  
 (d) -OCOR<sup>7</sup>,  
 (e) -SH,  
 (f) -SCOR<sup>7</sup>,  
 (g) -OCO<sub>2</sub>R<sup>8</sup>,  
 20 (h) -SCO<sub>2</sub>R<sup>8</sup>,  
 (i) OCONR<sup>7</sup><sub>2</sub>, and  
 (j) SCONR<sup>7</sup><sub>2</sub>;

each R<sup>5</sup> or R<sup>6</sup> is independently selected from the group consisting of

- 25 (a) hydrogen, and  
 (b) C<sub>1-4</sub>alkyl,

each R<sup>7</sup> is independently selected from the group consisting of

- (a) hydrogen and  
 (b) R<sup>8</sup>;

30 each R<sup>8</sup> is independently selected from the group consisting of

- (a) C<sub>1-6</sub>alkyl,  
 (b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>,

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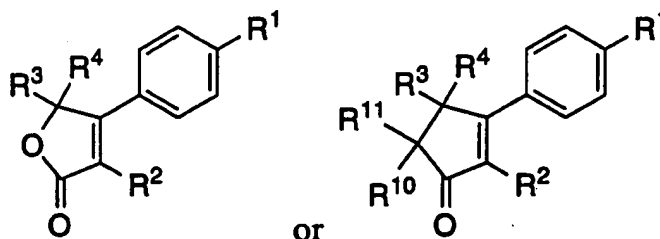
(c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkoxy, C<sub>1</sub>-4alkylthio, CN, or CF<sub>3</sub>;

R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of:

- (a) hydrogen ,
- (b) C<sub>1</sub>-10alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, C<sub>1</sub>-10fluoroalkyl, F or CONR<sup>7</sup><sub>2</sub>.

10. A compound according to Claim 8 of formula Ib or

Ic



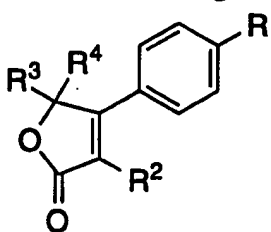
Ib

Ic

or a pharmaceutically acceptable salt thereof.

15

11. A compound according to Claim 10 of formula Ib



Ib

wherein

20 R<sup>2</sup> is a mono or di substituted heteroaryl wherein heteroaryl is selected from the group consisting of

- (1) furanyl,
- (2) diaziny, triaziny, tetraziny,
- (3) imidazolyl,
- (4) isooxazolyl,



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- 5 (5) isothiazolyl,  
(6) oxadiazolyl,  
(7) oxazolyl,  
(8) pyrazolyl,  
(9) pyrrolyl,  
(10) thiadiazolyl,  
(11) thiazolyl,  
(12) thienyl,  
(13) triazolyl, and  
10 (14) tetrazolyl,  
wherein the substituents are selected from the group  
consisting of  
(1) hydrogen,  
(2) fluoro or chloro,  
15 (3) C<sub>1</sub>-3alkoxy,  
(4) C<sub>1</sub>-6alkylthio,  
(5) CN,  
(6) CF<sub>3</sub>,  
(7) C<sub>1</sub>-3alkyl,  
20 (8) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH;  
(9) -C(R<sup>5</sup>)(R<sup>6</sup>)-O-C<sub>1</sub>-4alkyl.

12. A compound according to Claim 11 wherein  
R<sup>2</sup> is a mono or di substituted heteroaryl wherein heteroaryl is  
25 selected from the group consisting of  
(1) 2-furanyl,  
(2) 3-furanyl,  
(3) 2-thienyl,  
(4) 3-thienyl,  
30 (5) 3-isoxazolyl,  
(6) 4-isoxazolyl,  
(7) 5-isoxazolyl,  
(8) 3-isothiazolyl,  
(9) 4-isothiazolyl,

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- |    |                                 |
|----|---------------------------------|
|    | (10) 5-isothiazolyl,            |
|    | (11) 2-oxazolyl,                |
|    | (12) 4-oxazolyl,                |
|    | (13) 5-oxazolyl,                |
| 5  | (14) 2-thiazolyl,               |
|    | (15) 4-thiazolyl,               |
|    | (16) 5-thiazolyl,               |
|    | (17) 1,2,3-thiadiazol-4-yl,     |
|    | (18) 1,2,3-thiadiazol-5-yl,     |
| 10 | (19) 1,2,4-thiadiazol-3-yl,     |
|    | (20) 1,2,4-thiadiazol-5-yl,     |
|    | (21) 1,3,4-thiadiazol-2-yl,     |
|    | (22) 1,2,5-thiadiazol-3-yl,     |
|    | (23) 1,2,3-oxadiazol-4-yl,      |
| 15 | (24) 1,2,3-oxadiazol-5-yl,      |
|    | (25) 1,2,4-oxadiazol-3-yl,      |
|    | (26) 1,2,4-oxadiazol-5-yl,      |
|    | (27) 1,3,4-oxadiazol-2-yl,      |
|    | (28) 1,2,5-oxadiazol-3-yl,      |
| 20 | (29) pyrazol-4-yl,              |
|    | (30) pyrazol-5-yl,              |
|    | (31) 1,2,3-triadiazol-4-yl,     |
|    | (32) 1,2,3-triadiazol-5-yl,     |
|    | (33) 1,2,4-triadiazol-3-yl,     |
| 25 | (34) 1,2,4-triadiazol-5-yl,     |
|    | (35) 1,2-diazinyl,              |
|    | (36) 1,3-diazinyl,              |
|    | (37) 1,4-diazinyl,              |
|    | (38) 1,2,3,4-tetrazin-5-yl,     |
| 30 | (39) 1,2,4,5-tetrazin-4-yl,     |
|    | (40) 1,3,4,5-tetrazin-2-yl, and |
|    | (41) 1,2,3,5-tetrazin-4-yl.     |

13. A compound according to Claim 12 wherein

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R<sup>2</sup> is a mono or di substituted heteroaryl wherein heteroaryl is selected from the group consisting of

- |    |      |                        |
|----|------|------------------------|
|    | (1)  | 3-isoxazolyl,          |
|    | (2)  | 4-isoxazolyl,          |
| 5  | (3)  | 5-isoxazolyl,          |
|    | (4)  | 3-isothiazolyl,        |
|    | (5)  | 4-isothiazolyl,        |
|    | (6)  | 5-isothiazolyl,        |
|    | (7)  | 2-oxazolyl,            |
| 10 | (8)  | 4-oxazolyl,            |
|    | (9)  | 5-oxazolyl,            |
|    | (10) | 2-thiazolyl,           |
|    | (11) | 4-thiazolyl,           |
|    | (12) | 5-thiazolyl,           |
| 15 | (13) | 1,2,3-thiadiazol-4-yl, |
|    | (14) | 1,2,3-thiadiazol-5-yl, |
|    | (15) | 1,2,4-thiadiazol-3-yl, |
|    | (16) | 1,2,4-thiadiazol-5-yl, |
|    | (17) | 1,3,4-thiadiazol-2-yl, |
| 20 | (18) | 1,2,5-thiadiazol-3-yl, |
|    | (19) | 1,2,3-oxadiazol-4-yl,  |
|    | (20) | 1,2,3-oxadiazol-5-yl,  |
|    | (21) | 1,2,4-oxadiazol-3-yl,  |
|    | (22) | 1,2,4-oxadiazol-5-yl,  |
| 25 | (23) | 1,3,4-oxadiazol-2-yl,  |
|    | (24) | 1,2,5-oxadiazol-3-yl,  |
|    | (25) | 1,2-diazinyl,          |
|    | (26) | 1,3-diazinyl, and      |
|    | (27) | 1,4-diazinyl.          |

30

14. A compound according to Claim 13 wherein the heteroaryl is selected from the group consisting of

- (1) 3-isothiazolyl,
- (2) 4-isothiazolyl,

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- 5 (3) 5-isothiazolyl,  
 (4) 2-oxazolyl,  
 (5) 4-oxazolyl,  
 (6) 5-oxazolyl,  
 (7) 2-thiazolyl,  
 (8) 4-thiazolyl,  
 (9) 5-thiazolyl,  
 (10) 1,2-diazinyl,  
 (11) 1,3-diazinyl, and  
 10 (12) 1,4-diazinyl, and  
 wherein the substituents are selected from the group consisting of  
 (1) hydrogen,  
 (2) fluoro or chloro,  
 (3) C<sub>1</sub>-3alkoxy,  
 15 (4) C<sub>1</sub>-3alkylthio,  
 (5) CN,  
 (6) C<sub>1</sub>-3alkyl, and  
 (7) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,  
 R<sup>3</sup> is hydrogen, C<sub>1</sub>-4alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, or C<sub>1</sub>-4fluoroalkyl,  
 20 F, CONR<sup>7</sup><sub>2</sub>;  
 R<sup>4</sup> is  
 (a) C<sub>1</sub>-4alkoxy,  
 (b) C<sub>1</sub>-4alkylthio,  
 (c) -OH,  
 25 (d) -OCOR<sup>7</sup>,  
 (e) -SH,  
 (f) -SCOR<sup>7</sup>,  
 (g) -OCO<sub>2</sub>R<sup>8</sup>,  
 (h) -SCO<sub>2</sub>R<sup>8</sup>;  
 30 each R<sup>5</sup> or R<sup>6</sup> is independently selected from the group consisting of  
 (a) hydrogen, and  
 (b) C<sub>1</sub>-4alkyl,  
 each R<sup>7</sup> is independently selected from the group consisting of  
 (a) hydrogen and

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(b) R<sup>8</sup>;  
each R<sup>8</sup> is independently selected from the group consisting of

- 5 (a) C<sub>1</sub>-4alkyl,  
(b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkoxy, C<sub>1</sub>-4alkylthio, CN, or CF<sub>3</sub>.

15 15. A compound according to Claim 14 wherein the hetereoaryl is selected from the group consisting of

- 10 (1) 3-isothiazolyl,  
(2) 4-isothiazolyl,  
(3) 5-isothiazolyl,  
(4) 2-oxazolyl,  
(5) 4-oxazolyl,  
15 (6) 5-oxazolyl,  
(7) 2-thiazolyl,  
(8) 4-thiazolyl,  
(9) 5-thiazolyl,  
(10) 1,2-diazinyl,  
20 (11) 1,3-diazinyl, and  
(12) 1,4-diazinyl, and

wherein the substituents are selected from the group consisting of

- 25 (1) hydrogen,  
(2) fluoro or chloro,  
(3) C<sub>1</sub>-3alkoxy,  
(4) C<sub>1</sub>-3alkylthio,  
(5) CN,  
(6) C<sub>1</sub>-3alkyl, and  
(7) -C(R<sup>5</sup>)(R<sup>6</sup>)-OH,

30 R<sup>3</sup> is C<sub>1</sub>-3alkyl, CH<sub>2</sub>OR<sup>7</sup>, C<sub>1</sub>-4fluoroalkyl, F, CONR<sup>7</sup><sub>2</sub>;  
R<sup>4</sup> is

- (a) C<sub>1</sub>-3alkoxy,  
(b) C<sub>1</sub>-3alkylthio,  
(c) -OH,

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(d) -OCOR<sup>7</sup>,

(e) -SCOR<sup>7</sup>;

each R<sup>5</sup> or R<sup>6</sup> is independently selected from the group consisting of

(a) hydrogen, and

5 (b) C<sub>1</sub>-3alkyl,

each R<sup>7</sup> is independently selected from the group consisting of

(a) hydrogen and

(b) R<sup>8</sup>;

each R<sup>8</sup> is C<sub>1</sub>-3alkyl.

10

16. A compound according to claim 1 selected from the group consisting of

(1) Benzoic acid, 3-(4-(methylsulfonyl)phenyl)-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester,

15

(2) 5-Hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,

(3) 5-Hydroxy-3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

20

(4) 5-Hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,

(5) 3-(4-Fluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

(6) 3-(4-Chlorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

25

(7) 3-(3,4-Difluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

(8) 3-(3-Fluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

30

(9) 3-(3,5-Difluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

(10) 5-Methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,

(11) 3-(4-Chlorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

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- (12) 3-(3,4-Difluorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,  
 (13) 3-(3-Fluorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,  
 5 (14) 3-(3,5-Difluorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,  
 (15) 3-(4-Fluorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,  
 (16) 5-Ethoxy-3-(4-fluorophenyl)-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,  
 10 (17) 3-(4-Fluorophenyl)-5-methyl-4-(4-(methylsulfonyl)phenyl)-5-propoxy-2-(5H)-furanone,  
 (18) 3-(4-Fluorophenyl)-5-isopropoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,  
 15 (19) 5-Methyl-5-methylthio-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,  
 (20) 5-Ethylthio-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,  
 (21) 5-Ethyl-5-hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,  
 20 (22) 5-Ethyl-3-(3-fluorophenyl)-5-hydroxy-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone, and  
 (23) Acetic acid, 3-(4-(methylsulfonyl)phenyl)-5-methyl-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester  
 25 (24) 5-Hydroxy-5-methyl-4-((4-methylsulfonyl)phenyl)-3-(2-naphthyl)-2-(5H)-furanone,  
 (25) Sodium 2-(4-fluorophenyl)-3-((4-methylsulfonyl)phenyl)-4-oxo-2-pentenoate, and  
 (26) Sodium 2-(4-chlorophenyl)-3-((4-methylsulfonyl)phenyl)-4-oxo-2-pentenoate.  
 30

17. A pharmaceutical composition for treating an inflammatory disease susceptible to treatment with an non-steroidal anti-inflammatory agent comprising:

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a non-toxic therapeutically effective amount of a compound according to Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, and a pharmaceutically acceptable carrier.

5 18. A pharmaceutical composition for treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising: a non-toxic therapeutically effective amount of a compound according to Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, and a pharmaceutically acceptable carrier.

10 19. A method of treating an inflammatory disease susceptible to treatment with an non-steroidal anti-inflammatory agent comprising:  
administration to a patient in need of such treatment of a non-toxic  
15 therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

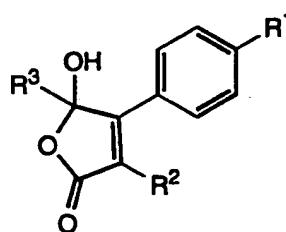
20 20. A method of treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:  
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to Claim 1.

25 21. A method of treating inflammation in a patient for which non-steroidal antiinflammatory drugs may be contra-indicated comprising:  
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

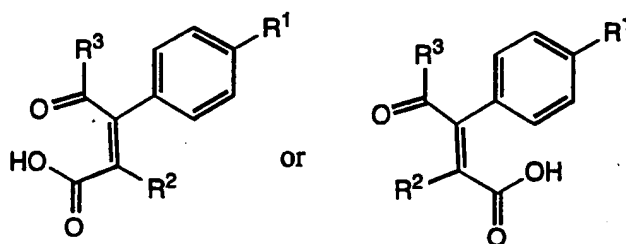
30 22. A compound according to Claim 1 of formula



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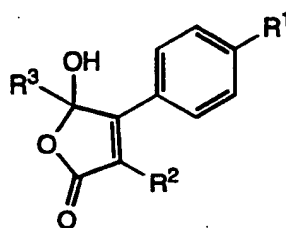


or tautomer thereof, which is



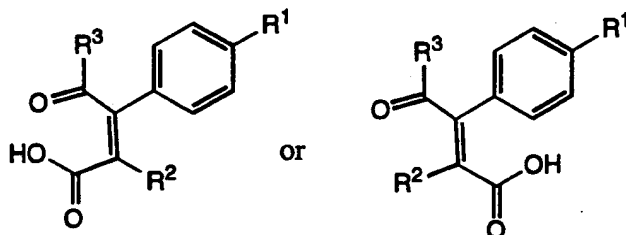
5

23. A compound according to Claim 7 of formula



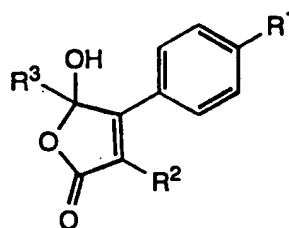
or tautomer thereof, which is

10

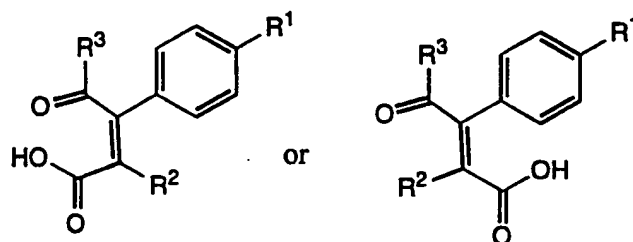


24. A compound according to Claim 8 of formula

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or tautomer thereof, which is



- 5            25. A pharmaceutically acceptable salt of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 22, 23 or 24.

- 10           26. A non-steroidal anti-inflammatory pharmaceutical composition comprising an acceptable, anti-inflammatory amount of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 17, 22, 23 or 24, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

- 15           27. A COX-2 selective inhibitor pharmaceutical composition comprising an acceptable COX-2 selectively inhibiting amount of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 22, 23 or 24, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

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28. A compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 22, 23 or 24, or a pharmaceutically acceptable salt thereof, for use in treating inflammation in a patient for which non-steroidal anti-inflammatory drugs may be contra-  
5 indicated.

29. Use of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 22, 23 or 24, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for treating cyclooxygenase mediated diseases advan-  
10 tagedously treated by an active agent that selective inhibits COX-2 in preference to COX-1.

30. Use of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 22, 23 or 24, or a pharmaceutically acceptable salt thereof, as an anti-inflammatory  
15 agent.

31. Use of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 22, 23 or 24, or a pharmaceutically acceptable salt thereof, as a selective inhibit of COX-  
2.

## INTERNATIONAL SEARCH REPORT

International Application No  
PC 1/CA 96/00306

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D307/60 A61K31/22 A61K31/38 A61K31/34 A61K31/365  
A61K31/41 C07D307/64 C07D405/04 C07D407/04 C07D409/04  
C07D417/04 C07C317/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,95 00501 (MERCK FROSST CANADA INC ;DUCHARME YVES (CA); GAUTHIER JACQUES YVES) 5 January 1995 cited in the application see abstract; claims; examples 12,56-60; table III see page 72, line 20 - line 25; table II see page 73, line 15 - line 22; table II ---	1-31
P,A	US,A,5 474 995 (DUCHARME YVES ET AL) 12 December 1995 cited in the application see abstract; claims 1,18-25; examples 13,56-60 -----	1-31

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search

16 August 1996

Date of mailing of the international search report

23. 08. 96

Name and mailing address of the ISA

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Authorized officer

Paisdor, B

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA96/00306

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark: Although claims 19-21 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No

PC1/CA 96/00306

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9500501	05-01-95	US-A- 5474995	12-12-95
		AU-B- 1269495	01-08-95
		AU-B- 6967494	17-01-95
		BR-A- 9406979	05-03-96
		CA-A- 2163888	05-01-95
		CA-A- 2176973	25-12-94
		CA-A- 2176974	25-12-94
		WO-A- 9518799	13-07-95
		EP-A- 0705254	10-04-96
		FI-A- 956119	19-12-95
		NO-A- 955256	23-02-96
		NO-A- 960393	09-07-96
		PL-A- 312196	01-04-96
		US-A- 5536752	16-07-96
		ZA-A- 9404501	13-03-95
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US-A-5474995	12-12-95	AU-B- 1269495	01-08-95
		AU-B- 6967494	17-01-95
		BR-A- 9406979	05-03-96
		CA-A- 2163888	05-01-95
		CA-A- 2176973	25-12-94
		CA-A- 2176974	25-12-94
		WO-A- 9500501	05-01-95
		WO-A- 9518799	13-07-95
		EP-A- 0705254	10-04-96
		FI-A- 956119	19-12-95
		NO-A- 955256	23-02-96
		NO-A- 960393	09-07-96
		PL-A- 312196	01-04-96
		US-A- 5536752	16-07-96
		ZA-A- 9404501	13-03-95
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